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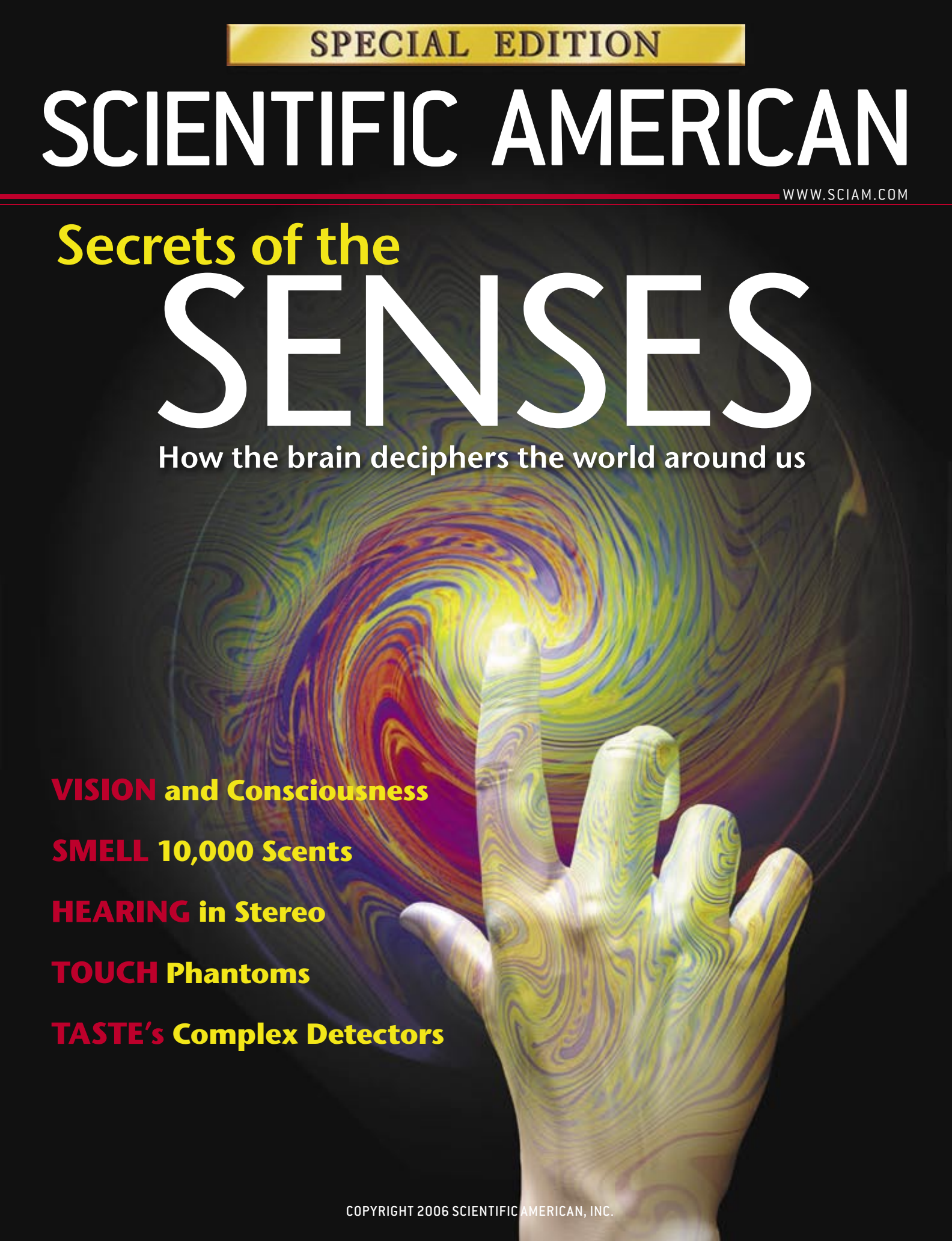
Secrets of the SENSES

How the brain deciphers the world around us



VISION and Consciousness

SMELL 10,000 Scents

HEARING in Stereo

TOUCH Phantoms

TASTE's Complex Detectors

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letter from the editor

Everyday Miracles

JEAN-FRANCOIS PODEVIN

IMAGINE what it must be like. In a condition called synesthesia, senses blend, with exotic effects. Each number may evoke its own color, and flavors can mingle with shapes—in one instance letting a man tell that a roasted chicken was done, because it tasted "pointy." In their article, "Hearing Colors, Tasting Shapes," starting on page 76, Vilayanur S. Ramachandran and Edward M. Hubbard describe how synesthesia has yielded insights into how the brain processes complex sensory inputs.

We take our conventional set of senses for granted, but their capabilities are no less astounding for their everyday qualities. The constant stream of data they provide helps the brain interpret our surroundings, giving us vital tools to survive and thrive. As Nobel Prize winner Richard Axel writes in "The Molecular Logic of Smell," beginning on page 68, humans "can recognize approximately 10,000 scents, ranging from the pleasurable scent of freshly cut flowers to the aversive smell of an angry skunk." Other senses leap into action to protect us from such foul-smelling danger. Interpreting acoustic signals from our two ears, the brain locates the rustling of an animal on the forest floor. At the same time, our visual systems near-instantly assemble into a coherent whole the scattered patches of black and white peeking through the leaves: "Skunk!"

When bereft of sensory feedback, the brain hastens to compensate, with revealing results. "Phantom Limbs," by Ronald Melzack, on page 52, describes the enduring mental presence of missing appendages, whereas "How the Blind Draw," by John M. Kennedy, on page 44, discusses a surprising connection between vision and touch.

As scientists try to make sense of our senses, they also seek to imitate or even improve on them to serve us in new ways. "Neuromorphic Microchips," by Kwabena Boahen, starting on page 20, describes work to etch visual systems in silicon for better artificial-recognition technologies. Kathryn S. Brown's story, which asks "Are You Ready for a New Sensation?", explores how biology is combining with engineering to design the sensory experiences of tomorrow; turn to page 60. These thought-provoking pieces, and the others in the issue, offer what we hope will be a sensational experience.

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secrets of the SENSES

CONTENTS

1 letter from the editor

SEE

4 vision: a window into consciousness
by nikos k. logothetis
In their search for the mind, scientists are focusing on visual perception—how we interpret what we see.

12 dying to see
by ralf dahm
Studies of the lens of the eye not only could reveal ways to prevent cataracts but also might illuminate the biology of Alzheimer's, Parkinson's and other diseases in which cells commit suicide.

20 neuromorphic microchips
by kwabena boahen
Compact, efficient electronics based on the brain's neural system could yield implantable silicon retinas to restore vision, as well as robotic eyes and other smart sensors.

HEAR

28 listening with two ears
by masakazu konishi
Studies of barn owls offer insight into just how the brain combines acoustic signals from two sides of the head into a single spatial perception.

36 music and the brain
by norman m. weinberger
What is the secret of music's strange power? Seeking an answer, scientists are piecing together a picture of what happens in the brains of listeners and musicians.

TOUCH

44 how the blind draw
by john m. kennedy
Blind and sighted people use many of the same devices in sketching their surroundings, suggesting that vision and touch are closely linked.

52 phantom limbs
by ronald melzack
People who have lost an arm or a leg often perceive the limb as though it were still there. Treating the pain of these ghostly appendages remains difficult.

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SCIENTIFIC AMERICAN
VOLUME 16, NUMBER 3 2006

The articles in this special edition are updated from previous issues of *Scientific American.*

SMELL

60 are you ready for a new sensation?
by kathryn s. brown
As biology meets engineering, scientists are designing the sensory experiences of a new tomorrow.

68 the molecular logic of smell
by richard axel
Mammals can recognize thousands of odors, some of which prompt powerful responses. Recent experiments illuminate how the nose and brain may perceive scents.

TASTE

76 hearing colors, tasting shapes
by vilayanur s. ramachandran and edward m. hubbard
People with synesthesia—whose senses blend together—are providing valuable clues to understanding the organization and functions of the brain.

84 making sense of taste
by david v. smith and robert f. margolskee
How do cells on the tongue register the sensations of sweet, salty, sour and bitter? Scientists are finding out—and discovering how the brain interprets these signals as various tastes.

Cover illustration by Jean-Francois Podevin.

page 60

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VISION: a window into CONSCIOUSNESS

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In their search for the mind, scientists are focusing on visual perception—how we interpret what we see

BY NIKOS K. LOGOTHETIS

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When you first look at the center image in the painting by Salvador Dalí reproduced at the left, what do you see? Most people immediately perceive a man's face, eyes gazing skyward and lips pursed under a bushy mustache. But when you look again, the image rearranges itself into a more complex tableau. The man's nose and white mustache become the mobcap and cape of a seated woman. The glimmers in the man's eyes reveal themselves as lights in the windows—or glints on the roofs—of two cottages nestled in darkened hillsides. Shadows on the man's cheek emerge as a child in short pants standing beside the seated woman—both of whom, it is now clear, are looking across a lake at the cottages from a hole in a brick wall, a hole that we once saw as the outline of the man's face.

In 1940, when he rendered *Old Age, Adolescence, Infancy (The Three Ages)*—which contains three "faces"—Dalí was toying with the capacity of the viewer's mind to interpret two different images from the same set of brushstrokes. More than 50 years later researchers, including my colleagues and me, are using similarly ambiguous visual stimuli to try to identify the brain activity that underlies consciousness. Specifically, we want to know what happens in the brain at the instant when, for example, an observer comprehends that the three faces in Dalí's picture are not really faces at all.

Consciousness is a difficult concept to define, much less to study. Neuroscientists have in recent years made impressive progress toward understanding the complex patterns of activity that occur in nerve cells, or neurons, in the brain. Even so, most people, including many scientists, still find the notion that electrochemical discharges in neurons can explain the mind—and in particular consciousness—challenging.

Yet, as the late Nobel laureate Francis Crick of the Salk Institute for Biological Studies in San Diego and Christof Koch of the California Institute of Technology have argued, the problem of consciousness can be broken down into several separate questions, some of which can be subjected to scientific inquiry. For example, rather than worrying about what consciousness is, one can ask: What is the difference between the neural processes that correlate with a particular conscious experience and those that do not?

Ambiguous stimuli, such as this painting by Salvador Dalí, entitled *Old Age, Adolescence, Infancy (The Three Ages),* aid scientists who use visual perception to study the phenomenon of consciousness.

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Now You See It ...

THAT IS WHERE ambiguous stimuli come in. Perceptual ambiguity is not a whimsical behavior specific to the organization of the visual system. Rather it tells us something about the organization of the entire brain and its way of making us aware of all sensory information. Take, for instance, the meaningless string of French words *pas de lieu Rhône que nous,* cited by psychologist William James in 1890. You can read this over and over again without recognizing that it sounds just like the phrase "paddle your own canoe." What changes in neural activity occur when the meaningful sentence suddenly reaches consciousness?

In our work with ambiguous visual stimuli, we use images that not only give rise to two distinct perceptions but also instigate a continuous alternation between the two. A familiar example is the Necker cube [*see illustration on this page*]. This figure is perceived as a three-dimensional cube, but the apparent perspective of the cube appears to shift every few seconds. Obviously, this alternation must correspond to something happening in the brain.

A skeptic might argue that we sometimes perceive a stimulus without being truly conscious of it, as when, for example, we "automatically" stop at a red light when driving. But the stimuli and the situations that I investigate are actually designed to reach consciousness.

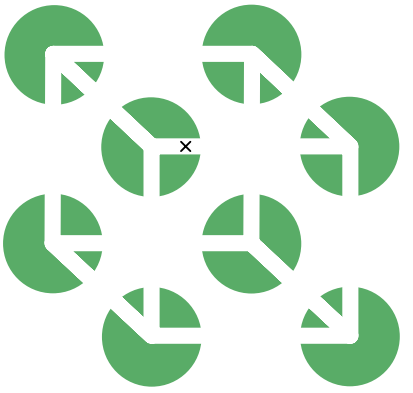
We know that our stimuli reach awareness in human beings, because they can tell us about their experience. But it is not usually possible to study the activity of individual neurons in awake humans, so we perform our experiments with alert monkeys that have been trained to report what they are perceiving by pressing levers or by looking in a particular direction. Monkeys' brains are organized like those of humans, and they respond to such stimuli much as humans do. Consequently, we think the animals are conscious in somewhat the same way as humans are.

We investigate ambiguities that result when two different visual patterns are presented simultaneously to each eye, a phenomenon called binocular rivalry. When people are put in this situation, their brains become aware first of one perception and then the other, in a slowly alternating sequence [*see box on opposite page*].

In the laboratory, we use stereoscopes to create this effect. Trained monkeys exposed to such visual stimulation report that they, too, experience a perception that changes every few seconds. Our experiments have enabled us to trace neural activity that corresponds to these changing reports.

In the Mind's Eye

STUDIES OF NEURAL ACTIVITY in animals conducted over several decades have established that visual information leaving the eyes ascends through successive stages of a neural data-processing system. Different modules analyze various attributes of the visual field. In general, the type of processing becomes more specialized the farther the information moves along the visual pathway [*see illustration on page 8*].



Necker cube can be viewed two different ways, depending on whether you see the "x" on the top front edge of the cube or on its rear face. Sometimes the cube appears superimposed on the circles; other times it seems as if the circles are holes and the cube is floating behind the page.

At the start of the pathway, images from the retina at the back of each eye are channeled first to a pair of small structures deep in the brain called the lateral geniculate nuclei (LGN). Individual neurons in the LGN can be activated by visual stimulation from either one eye or the other but not both. They respond to any change of brightness or color in a specific region within an area of view known as the receptive field, which varies among neurons.

From the LGN, visual information moves to the primary visual cortex, known as V1, which is at the back of the head. Neurons in V1 behave differently than those in the LGN do. They can usually be activated by either eye, but they are also sensitive to specific attributes, such as the orientation of a contour or the direction of motion of a stimulus placed within their receptive field. Visual information is transmitted from V1 to more than two dozen other distinct cortical regions, called the extrastriate visual areas.

Some information from V1 can be traced as it moves through areas known as V2 and V4 before winding up in regions known as the inferior temporal cortex (ITC), which like all the other structures are bilateral. A large number of investigations, including neurologi-

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NIKOS K. LOGOTHETIS is director of the physiology of cognitive processes department at the Max Planck Institute (MPI) for Biological Cybernetics in Tübingen, Germany. He received his Ph.D. in human neurobiology in 1984 from Ludwig-Maximillians University in Munich. He then moved to the brain and cognitive sciences department of the Massachusetts Institute of Technology, and in 1990 he joined the faculty of the division of neuroscience at Baylor College of Medicine. Seven years later he moved to MPI to continue his work on visual perception. His recent research includes the application of functional magnetic resonance imaging (fMRI) to monkeys and measurement of how the fMRI signal relates to neural activity. Since 1992 he has been adjunct professor of neurobiology at the Salk Institute for Biological Studies in San Diego; since 1995, adjunct professor of ophthalmology at Baylor; and since 2002, an associate of the Neurosciences Institute in San Diego and senior visiting fellow at University College London. This year he became a part-time faculty member at the Victoria University of Manchester in England. Logothetis is a recipient of the DeBakey Award for Excellence in Science, the Golden Brain Award of the Minerva Foundation, the 2003 Louis-Jeantet Prize of Medicine and the Zülch Prize for Neuroscience.

NOSNHOJ ANNHOJ

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cal studies of people who have experienced brain damage, suggest that the ITC is important in perceiving form and recognizing objects. Neurons in V4 are known to respond selectively to aspects of visual stimuli critical to discerning shapes. In the ITC, some neurons behave like V4 cells, but others respond only when entire objects, such as faces, are placed within their very large receptive fields.

Other signals from V1 pass through regions V2, V3 and an area known as V5/MT (the medial temporal cortex) before eventually reaching a part of the brain called the parietal lobe. Most neurons in V5/MT respond strongly to items moving with a specific velocity; we say they are speed- and direction-selective. Neurons in other areas of the parietal lobe respond when an animal pays attention to a stimulus or intends to move toward it.

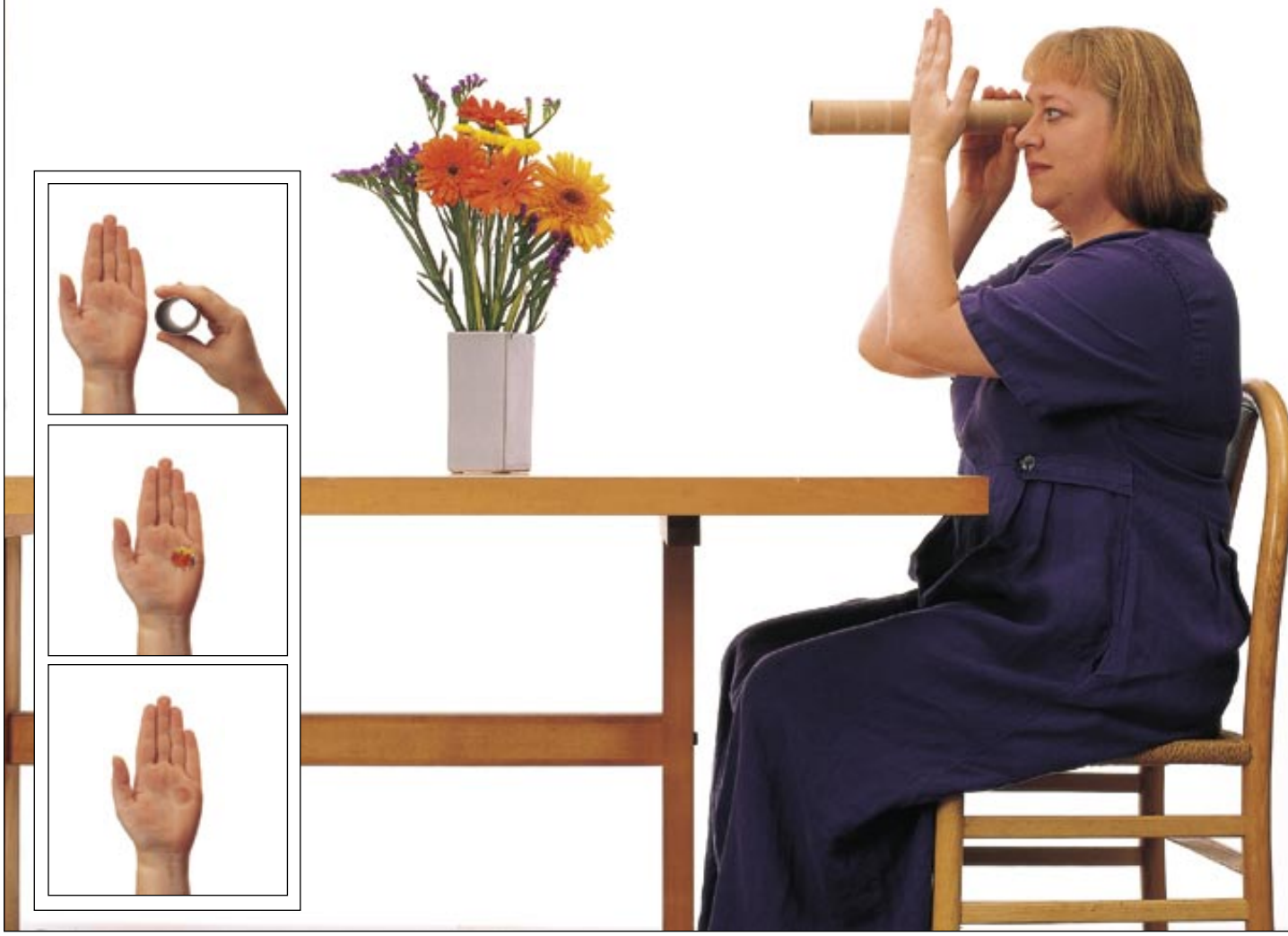
One surprising observation made in early experiments is that many neurons in these visual pathways, both in V1 and in higher levels of the processing

How to Experience Binocular Rivalry

To simulate binocular rivalry at home, use your right hand to hold the cardboard cylinder from a roll of paper towels (or a piece of paper rolled into a tube) against your right eye. Hold your left hand, palm facing you, roughly four inches in front of your left eye, with the edge of your hand touching the tube.

At first it will appear as though your hand has a hole in it, as your brain concentrates on the stimulus from your right eye. After a few seconds, though, the "hole" will fill in with a fuzzy perception of your whole palm from your left eye. If you keep looking, the two images will alternate, as your brain selects first the visual stimulus viewed by one eye, then that viewed by the other. The alternation is, however, a bit biased; you will probably perceive the visual stimulus you see through the cylinder more frequently than you will see your palm.

The bias occurs for two reasons. First, your palm is out of focus because it is much closer to your face, and blurred visual stimuli tend to be weaker competitors in binocular rivalry than sharp patterns, such as the surroundings you are viewing through the tube. Second, your palm is a relatively smooth surface with less contrast and fewer contours than your comparatively rich environment. In the laboratory, we carefully select the patterns viewed by the subjects to eliminate such bias. —*N.K.L.*



DAN WAGNER

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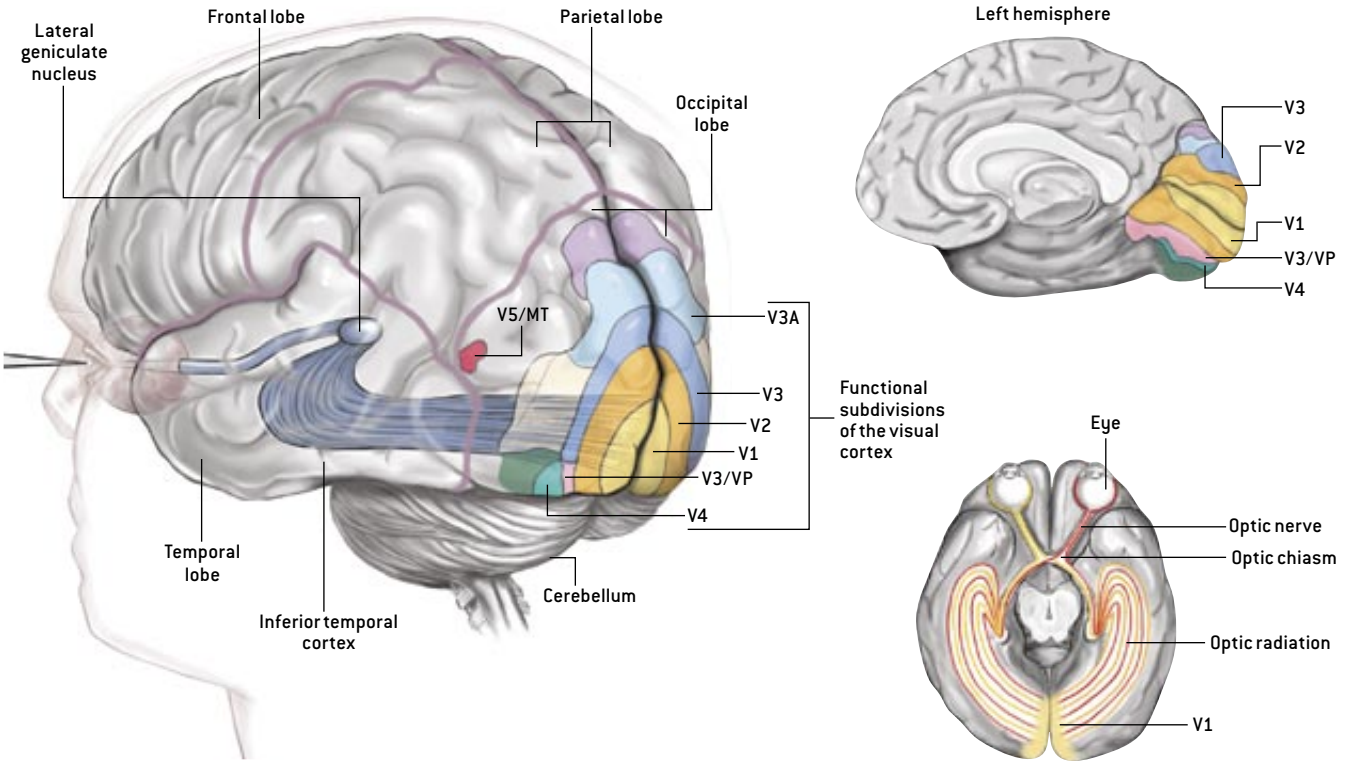
Structures for Seeing

Human visual pathway begins with the eyes and extends through several interior brain structures before ascending to the various regions of the primary visual cortex (V1, and so on). At the optic chiasm, the optic nerves cross over partially so that each hemisphere of the brain receives input from both eyes. The information is filtered by the lateral geniculate nucleus, which consists of layers of nerve cells that each respond only to stimuli from one eye. The inferior temporal cortex is important for seeing forms. Some cells from each area are active only when a person or monkey becomes conscious of a given stimulus.



hierarchy, still respond with their characteristic selectivity to visual stimuli even in animals that have been completely anesthetized. Clearly, an animal (or a human) is not conscious of all neural activity.

The observation raises the question of whether awareness is the result of the activation of special brain regions or clusters of neurons. The study of binocular rivalry in alert, trained monkeys allows us to approach that question, at least to some extent. In such experiments, each animal is presented with a variety of visual stimuli, usually patterns or figures projected onto a screen. Monkeys can easily be trained to report accurately what stimulus they perceive by means of rewards of fruit juice [*see box on pages 10 and 11*].

During the experiment, the scientist uses electrodes to record the activity of neurons in the visual-processing pathway. Neurons vary markedly in their responsiveness when identical stimuli are presented to both eyes simultaneously. Stimulus pattern A might provoke activity in one neuron, for instance, whereas stimulus pattern B does not.

Once an experimenter has identified an effective and an ineffective stimulus for a given neuron (by presenting the same stimulus to both eyes at once), the two stimuli can be presented so that a different one is seen by each eye. We expect that, like a human in this situation, the monkey will become aware of the two stimuli in an alternating sequence. And, indeed, that is what the monkeys tell us by their responses when we present them with such rivalrous pairs of stimuli. By recording from neurons during successive presentations of rivalrous pairs, an experimenter can evaluate which neurons change their activity only when the stimuli change and which neurons alter their rate of firing when the animal reports a changed perception that is not accompanied by a change in the stimuli.

Jeffrey D. Schall, now at Vanderbilt University, and I carried out a version of this experiment in which one eye saw a grating that drifted slowly upward while the other eye saw a downward-moving grating. We recorded from visual area V5/MT. We found that about 43 percent of the cells in this area changed their level of activity when the monkey indicated that its perception had changed from up to down, or vice versa. Most of these cells were in the deepest layers of V5/MT.

The percentage we measured was actually a lower proportion than most scientists would have guessed, because

TERESE WINSLOW, WITH ASSISTANCE FROM HEIDI BASELER, BILL PRESS AND BRIAN WANDELL *Stanford University*

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almost all neurons in V5/MT are sensitive to direction of movement. The majority of neurons in V5/MT did behave somewhat like those in V1, remaining active when their preferred stimulus was in view of either eye, whether it was being perceived or not.

There were further surprises. Some 11 percent of the neurons examined were excited when the monkey reported perceiving the more effective stimulus of an upward/downward pair for the neuron in question. But, paradoxically, a similar proportion of neurons was most excited when the most effective stimulus was not perceived—even though it was in clear view of one eye. Other neurons could not be categorized as preferring one stimulus over another.

While we were both at Baylor College of Medicine, David A. Leopold and I studied neurons in parts of the brain known to be important in recognizing objects. (Leopold came with me to the Max Planck Institute [MPI] for Biological Cybernetics in Tübingen, Germany, and in 2004 he moved to the National Institute of Mental Health [NIMH] where he continues research on perception using both physiological techniques and functional magnetic resonance imaging [fMRI]. This neuroimaging technique yields pictures of brain activity by measuring increases in blood flow in specific areas of the brain.) We recorded activity in V4, as well as in V1 and V2, while animals viewed stimuli consisting of lines sloping either to the left or to the right. In V4 the proportion of cells whose activity reflected perception was similar to that which Schall and I had found in V5/MT, around 40 percent. But again, a substantial proportion fired best when their preferred stimulus was not perceived. In V1 and V2, in contrast, fewer than one in 10 of the cells fired exclusively when their more effective stimulus was perceived, and none did so when it was not perceived.

While at MPI, Leopold—together with our students Alexander Maier and Melanie Wilke (now both at the NIMH)—demonstrated that the neural response patterns we found by using stimuli-inducing binocular rivalry can also be obtained when the animals view other types of ambiguous visual patterns (for example, displays of objects with ambiguous three-dimensional appearance), which do not involve any local interocular competition. All in all, our recording of multiple-unit activity in the early extrastriate cortical areas showed that different perceptual states correlate with subtle but significant changes in the activity of large populations of cells.

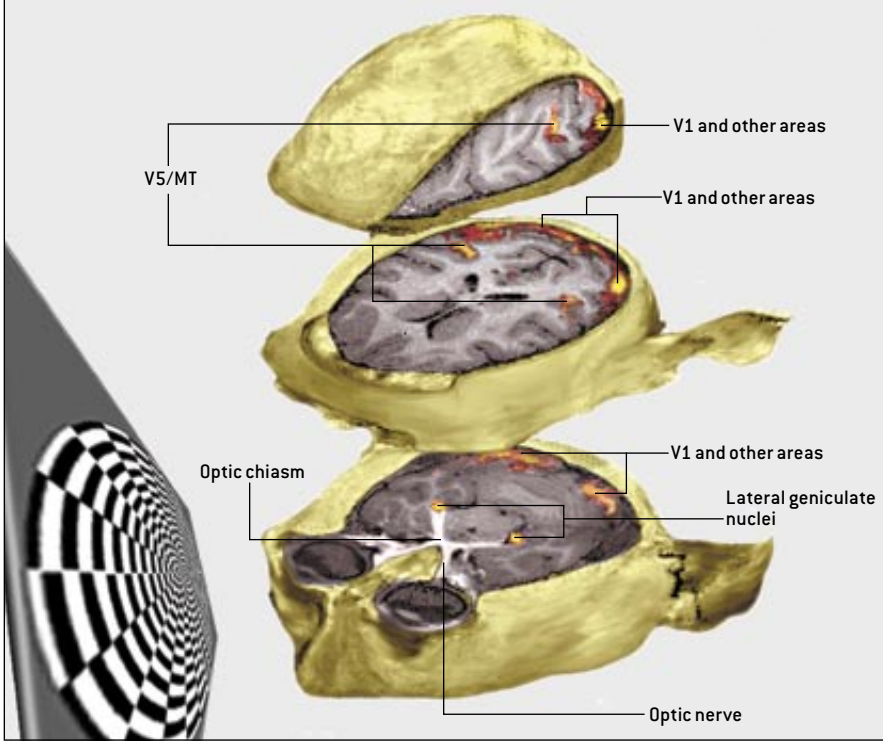
The pattern of activity was entirely different in the ITC. David L. Sheinberg, now at Brown University, and I recorded from this area after training monkeys to report their perceptions during rivalry between complex visual patterns, such as images of humans, animals and various man-made objects. We found that almost all neurons, about 90 percent, responded vigorously when their preferred pattern was perceived but that their activity was profoundly inhibited when this pattern was not being experienced. So it seems that by the time visual signals reach the ITC, the great majority of neurons are responding in a way that is linked to perception.

In short, most of the neurons in the earlier stages of the visual pathway responded mainly to whether their preferred visual stimulus was in view or not, although a few showed behavior that could be related to changes in the animal's perception. In the later stages of processing, on the other hand, the proportion whose activity reflected the animal's perception increased until it reached 90 percent.

A critic might object that the changing perceptions that monkeys report during binocular rivalry could be caused by the brain suppressing visual information at the start of the visual pathway, first from one eye and then from the other, so that the brain perceives a single image at any given time. If that were happening, changing neural activity and

Unconscious Vision

Images of brain activity are from an anesthetized monkey that was presented with a rotating, high-contrast visual stimulus (*lower left*). These views, taken using functional magnetic resonance imaging, show that even though the monkey is unconscious, its vision-processing areas—including the lateral geniculate nuclei, primary visual cortex (V1) and medial temporal cortex (V5/MT)—are busy.



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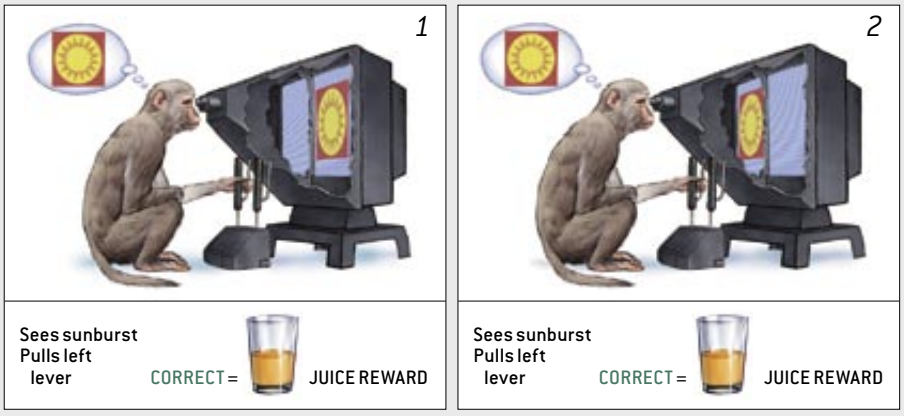
Keeping Monkeys (and Experimenters) Honest

One possible objection to the experiments described in the main article is that the monkeys might have been inclined to cheat to earn their juice rewards. We are, after all, unable to know directly what a monkey (or a human) thinks or perceives at a given time. Because our monkeys were interested mainly in drinking juice rather than in understanding how consciousness arises from neuronal activity, it is possible that they could have developed a response strategy that appeared to reflect their true perceptions but really did not.

In the training session depicted in 1–3, for example, the monkey was being taught to pull the left lever only when it saw a sunburst and the right lever only when it saw a cowboy. We were able to ensure that the monkey continued to report truthfully by interjecting instances in which no rivalrous stimuli were shown (*4*). During these occasions, there was a "right" answer to what was perceived, and if the monkey did not respond correctly, the trial—and thus the opportunity to earn more juice rewards—



perceptions would simply represent the result of input that had switched from one eye to the other and would not be relevant to visual consciousness in other situations. But experimental evidence shows decisively that input from both eyes is continuously processed in the visual system during binocular rivalry.

We know this because it turns out that in humans, binocular rivalry produces its normal slow alternation of perceptions even if the competing stimuli are switched rapidly—several times per second—between the two eyes. If rivalry were merely a question of which eye the brain is paying attention to, the rivalry phenomenon would vanish when stimuli are switched quickly in this way. (The viewer would see, rather, a rapid alternation of the stimuli.) The observed persistence of slowly changing rivalrous perceptions when stimuli are switched strongly suggests that rivalry occurs because alternate stimulus representations compete in the visual pathway. Binocular rivalry thus affords an opportunity to study how the visual system decides what we see even when both eyes see (almost) the same thing.

A Perceptual Puzzle

WHAT DO THESE FINDINGS reveal about visual awareness? First, they show that we are unaware of a great deal of activity in our brains. We have long known that we are mostly unaware of the activity in the brain that maintains the body in a stable state—one of its evolutionarily most ancient tasks. Our experiments show that we are also unaware of much of the neural activity that generates—at least in part—our conscious experiences.

We can say this because many neurons in our brains respond to stimuli that we are not conscious of. Only a tiny fraction of neurons seem to be plausible candidates for what physiologists call the "neural correlate" of conscious perception—that is, they respond in a manner that reliably reflects perception.

We can say more. The small number of neurons whose behavior reflects perception are distributed over the entire visual pathway, rather than being part of a single area in the brain. The changes in the activity of such neurons during a perceptual transition are small relative to those observed during the physical alternation of the stimuli. Yet such small changes in the response of a distributed neuronal population result in robust alternating patterns of excitation and inhibition of ITC cells during the perceptual dominance and suppression of a pattern, respectively. Although the ITC clearly has many more neurons that behave this way than those in other regions do, such neurons may be found elsewhere in future experiments. Moreover, other brain regions may be responsible for any decision resulting from whatever stimulus reaches consciousness. Erik D. Lumer and his colleagues at University College London have studied that possibility using fMRI. They showed that in humans the temporal lobe is activated during the conscious experience of a stimulus, as we found in monkeys. But other regions, such as the parietal and the prefrontal cortical areas, are activated precisely at the time at which a subject reports that the stimulus changes.

Further data about the locations of and connections between neurons that correlate with conscious experience will tell us more about how the brain generates awareness. But the findings to date already strongly suggest that visual awareness cannot be thought of as the end product of such a hierarchical series of processing stages. Instead it involves the entire visual pathway as well as the frontal parietal areas, which are involved in higher cognitive processing. The activity of a significant minority of neurons reflects what is consciously seen even in the lowest levels we looked at, V1 and V2; it is only the proportion of active neurons that increases at higher levels in the pathway.

It is not clear whether the activity of neurons in the very early areas is determined by their connections with other neurons in those areas or is the result of

MATT COLLINS

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was immediately ended. Similarly, if the monkey pulled any lever when presented with a jumbled image, in which the sunburst and the cowboy were superimposed (5), we knew the monkey was lying in an attempt to get more juice. Our results indicate that monkeys report their experiences accurately. Even more convincing is our observation that monkeys and humans tested with the same apparatus perform at similar levels in different tasks. —*N.K.L.*

top-down, "feedback" connections emanating from the temporal or parietal lobes. Visual information flows from higher levels down to the lower ones as well as in the opposite direction. Theoretical studies indicate that systems with this kind of feedback can exhibit complicated patterns of behavior, including multiple stable states. Different stable states maintained by top-down feedback may correspond to different states of visual consciousness. Neuroimaging studies with human subjects can afford the use of elaborated behavioral paradigms designed to discriminate such top-down from bottom-up processes, but the fMRI signal is mainly sensitive to the input and local processing in each area. Such local activation may or may not excite the large cells (for instance, the pyramidal neurons of cortex) that represent the area's output and are typically isolated and studied in behaving animals.

One important question is whether the activity of any of the neurons we have identified truly determine an animal's conscious perception. It is, after all, conceivable that these neurons are merely under the control of some other unknown part of the brain that actually determines conscious experience.

Elegant experiments conducted by William T. Newsome and his colleagues at Stanford University suggest that in area V5/MT, at least, neuronal activity can indeed determine directly what a monkey perceives. Newsome first identified neurons that selectively respond to a stimulus moving in a particular direction, then artificially activated them with small electric currents. The monkeys reported perceiving motion corresponding to the artificial activation even when stimuli were not moving in the direction indicated.

It will be interesting to see whether neurons of different types, in the ITC and possibly in lower levels, are also directly implicated in mediating consciousness. If they are, we would expect that stimulating or temporarily inactivating them would change an animal's reported perception during binocular rivalry.

A fuller account of visual awareness will also have to consider results from experiments on other cognitive processes, such as attention or what is termed working memory. Experiments by Robert Desimone and his colleagues at the NIMH reveal a remarkable resemblance between the competitive interactions observed during binocular rivalry and processes implicated in attention. Desimone and his colleagues train monkeys to report when they see stimuli for which they have been given cues in advance. Here, too, many neurons respond in a way that depends on what stimulus the animal expects to see or where it expects to see it. It is of obvious interest to know whether those neurons are the same ones as those firing only when a pattern reaches awareness during binocular rivalry.

The picture of the brain that starts to emerge from these studies is of a system whose processes create states of consciousness in response not only to sensory inputs but also to internal signals representing expectations based on past experiences. In principle, scientists should be able to trace the networks that support these interactions. The task is huge, but our success in identifying neurons that reflect consciousness is a good start. SA

MORE TO EXPLORE

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SIGHT

DYING TO SEE

Studies of the lens of the eye not only could reveal ways to prevent cataracts but also might illuminate the biology of Alzheimer's, Parkinson's and other diseases in which cells commit suicide

BY RALF DAHM

Aging and damage to the eye's lens can cause cataracts and yellowing that ruin vision, which may put the viewer at risk.

RENEE LYNN *Corbis (impalas and lionesses)*; JANA BRENNING *(photocomposition)*

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The lens of the eye is a uniquely transparent tissue in the human body. In the past few years, scientists have determined that this transparency—critical for focusing light—stems in large part from the unique ability of the lens to activate a self-destruct program in its cells that aborts just before completion, leaving empty but sustainable cells that transmit visible rays.

A better understanding of how lens cells become and remain transparent should suggest ways to prevent lens-clouding cataracts. More than half of all Americans older than 65 develop these sight-blocking occlusions. The only recourse is to surgically remove the person's lens and insert an artificial implant, and even then, complications requiring a second operation occur in a large proportion of patients. Given that cataracts affect primarily older people, for whom any kind of surgery is worrisome, a method to slow, stop or reverse cataracts would be a great aid indeed.

Beyond protecting vision, improved knowledge of how the lens tightly controls cell suicide could reveal ways to treat debilitating conditions characterized by excessive or inappropriate cell death, chief among them Parkinson's disease, Alzheimer's disease and chronic infections such as AIDS.

Barely Alive

THE EYE'S LENS is a biological marvel, being at once dense, flexible and clear. If it bore the slightest obscurities, our visual world would be a fun house of warped and blurred images and glare. And if the lens had any hint of color, it would absorb light, preventing us from seeing certain shades.

Many animals possess translucent parts, such as insect wings, but truly transparent tissue in nature is rare and difficult to achieve. In humans the cornea is clear, but it is mostly composed of gelatinous layers of proteins and sugars and contains only a few cells. The lens, however, is composed of about 1,000 layers of perfectly clear, living cells. Other than vision, the only significant exploitation of transparency in the natural world occurs among certain ocean and freshwater creatures, which use the trait to blend into the open water and hide from predators. Yet almost all these animals, such as jellyfish, qualify only as "very translucent," not totally see-through.

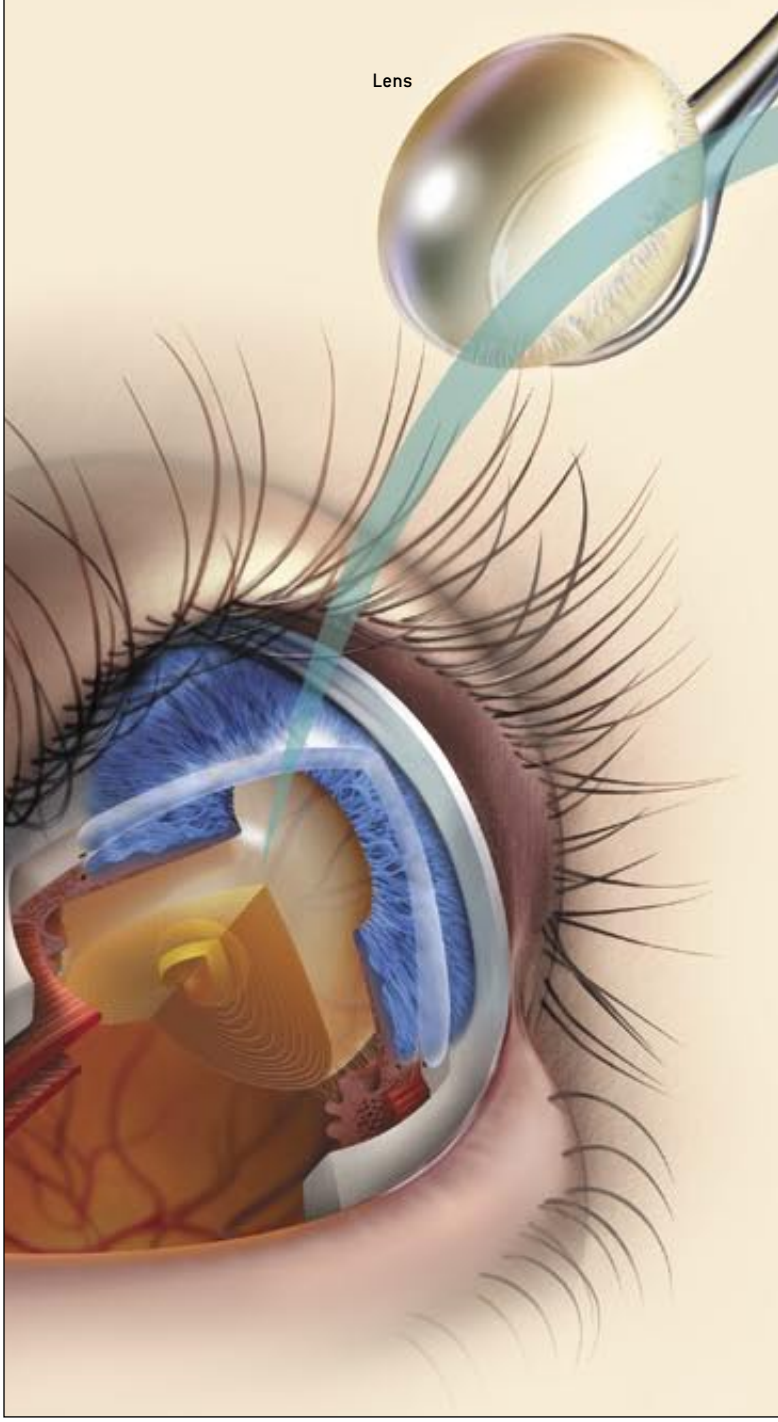
Transparency is unusual because cells have organelles—internal structures such as the nucleus (which stores DNA), the energy-producing mitochondria, and the Golgi apparatus and endoplasmic reticulum, which are important in the synthesis of proteins and lipids. Each structure has its own refractive index, and when a light ray crosses an area where the index changes, the light scatters, creating a degree of opaqueness.

In addition, some cells absorb certain wavelengths of light, resulting in color. The heme of the hemoglobin in blood cells gives them their characteristic red hue. Because organs and muscles have a blood supply, they appear primarily in shades of red, too. Furthermore, many cells, especially those in hair and skin, are populated with melanins—pigment molecules that come in colors ranging from red to black.

The lens has no melanins and no blood supply. Yet that

The Lens: Killing Itself for Clarity

The eye lens is transparent both because of its architecture and because of its unusual developmental program. The cells of the fully formed lens fit together in a regular arrangement that limits the scattering of light *(diagram at right* and *micrographs at far right*). And those cells become free of light-obstructing material during development (*bottom right*) by initiating a suicide program that dissolves their innards but halts before the cells actually die.



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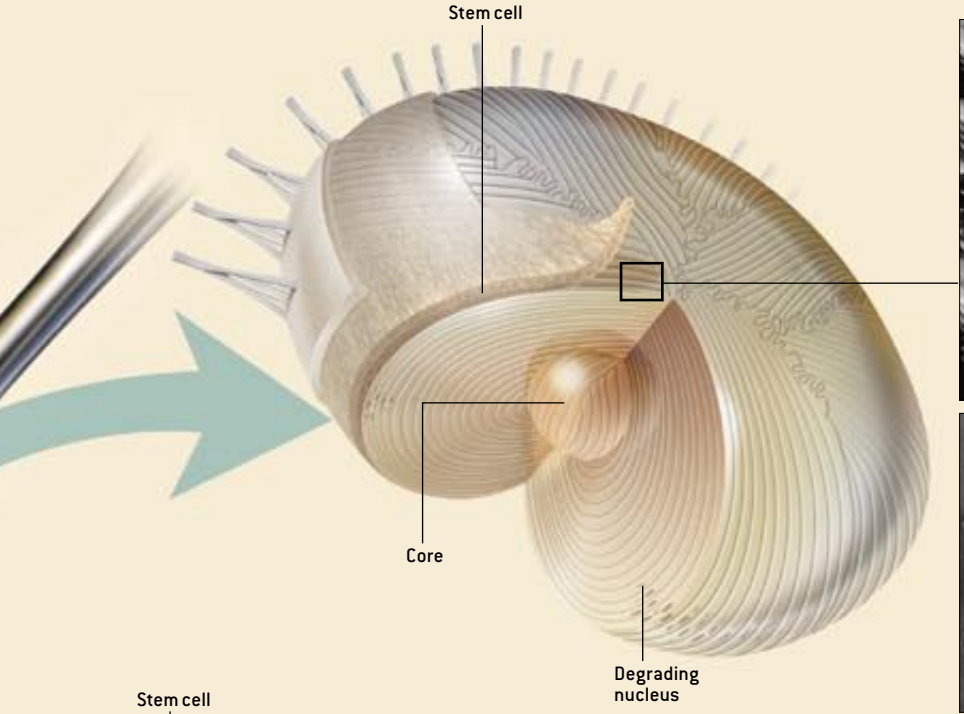
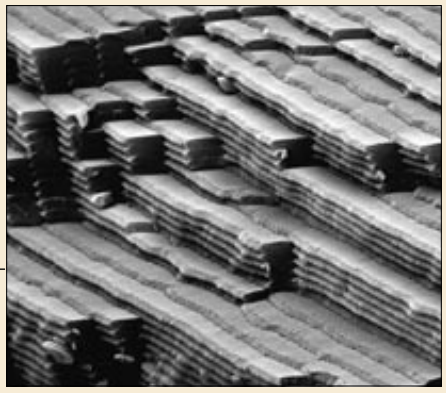
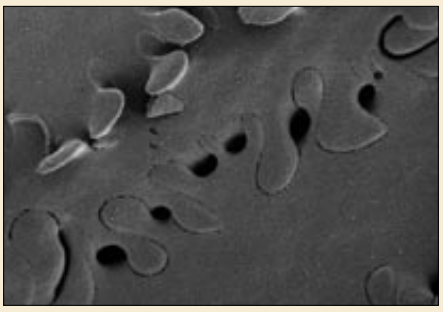




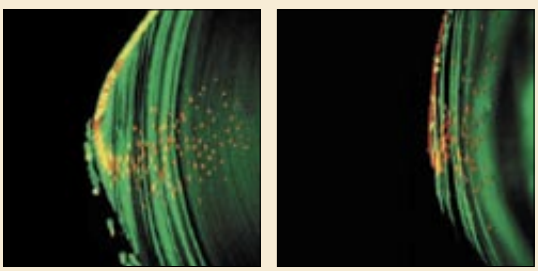


Layers of lens cells align in parallel (*top*), so that light passes perpendicularly through them, as in this bovine lens. Within a layer (*bottom*), adjacent cells interlock like jigsaw puzzle pieces to prevent gaps from forming when the lens changes shape during focusing; the layering and interlocking of cells enable light to pass across cell boundaries without scattering.

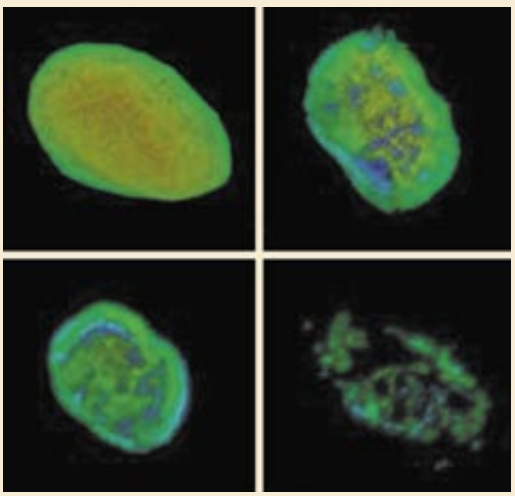
The Developing Lens

Lens development begins in early embryos when undifferentiated (stem) cells lining a spherical vesicle (*left, top*) differentiate into lens cells that reach across the cavity (*left, bottom*). After this core forms, more stem cells differentiate into cells that elongate around the outside rim, adding layers in an onionlike manner (*above*). Initially these cells have a nucleus, mitochondria, endoplasmic reticulum and other typical organelles. But as they are encapsulated by newer cells, they degrade their organelles, leaving nothing but an outer membrane and a thick solution of special proteins called crystallins. This barely living material has a uniform index of refraction, so it does not scatter light.

Aspects of the process can be seen in a developing lens (*below, left*) and in a nearly fully developed lens (*below, right*) of a mouse. New cells stretch down across the equatorial region and effectively move inward as even newer cells cover them. Cell nuclei (*red*) traveling down and in persist for a time but dissolve as they are buried.



The nucleus of a developing lens cell dissolves over several days (*below*), with the nuclear envelope and DNA inside breaking down in tandem.



KEITH KASNOT (*drawings*); RALF DAHM (*top SEM, layers*); ALAN R. PRESCOTT *University of Dundee, Scotland* (*bottom SEM, jigsaw pieces*); FROM "DEVELOPMENT OF A MACROMOLECULAR DIFFUSION PATHWAY IN THE LENS," BY Y. I. SHESTOPALOV AND S. BASSNETT, IN *JOURNAL OF CELL SCIENCE*, VOL. 15, 2003 (*bottom left two images, nucleated cells*); RALF DAHM (*bottom right four images, degrading nuclei*)

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alone is not enough for transparency. Cartilage has no melanins or blood supply and is colorless, but it is at best translucent. That is because in virtually all tissues, cells or fibers are oriented at various angles, creating different refractive indices that scatter light as it passes through. The lens is composed of only one cell type, and the cells are precisely aligned.

Given that lens cells have no blood supply, no connective or nervous tissue, and no organelles, can they even be considered alive? The answer depends on how "life" is defined. Lots of small animals without a blood supply are happily populating the planet. Human cartilage receives no blood, but any biologist would consider it living. If life means a cell has a metabolism, then lens cells are alive—albeit barely. Although they have no mitochondria to produce energy, certain nutrients and other molecules diffuse into the lens's outermost cells and slowly pass inward, cell to cell.

Young lens cells do have organelles when they first form from stem cells in a fetus, but the organelles are destroyed during early development. (The same occurs for new cells that are periodically laid down during adulthood.) What remains is a cytoplasm consisting of an unusually thick solution of special proteins called crystallins. Although the lens is often described as a crystal, it does not qualify in the chemical sense—where the geometric position of ions or molecules with respect to one another is systematically repeated. The lens is a "biological crystal"—that is, it has a very regular arrangement of cells. Each cell contains large molecules—crystallin proteins—that form complexes with paracrystalline arrangements. This construction makes the cytoplasm optically homogeneous; the refractive index does not change inside the cell or from one cell to another.

Seeing through a Glass, Dimly

CLARITY, OF COURSE, comes at a cost. Although lens cells survive the controlled suicide of organelles, this degradation has drastic implications. Without nuclei, the genetic programs for synthesizing new parts are gone. Mature lens cells cannot regenerate or repair themselves, as cells in other tissues do.

The ability to replace damaged parts is a prime advantage of biological systems. The molecules that compose human cells typically have half-lives lasting a few minutes to several days. Within six months or so, 90 percent of the molecules that make up our bodies are replaced by new ones. Lens cells, however, must function for a lifetime—a spectacular span.

This lack of repair mechanism makes the cells vulnerable to certain stresses. For example, severe dehydration can cause crystallin proteins to precipitate, prompting their cells to crumble into a clump—a cataract. This speck disrupts the otherwise uniform index of refraction, creating a cloudy spot in a person's field of vision. Just a few weeks of extreme dehydration can initiate cataract formation.

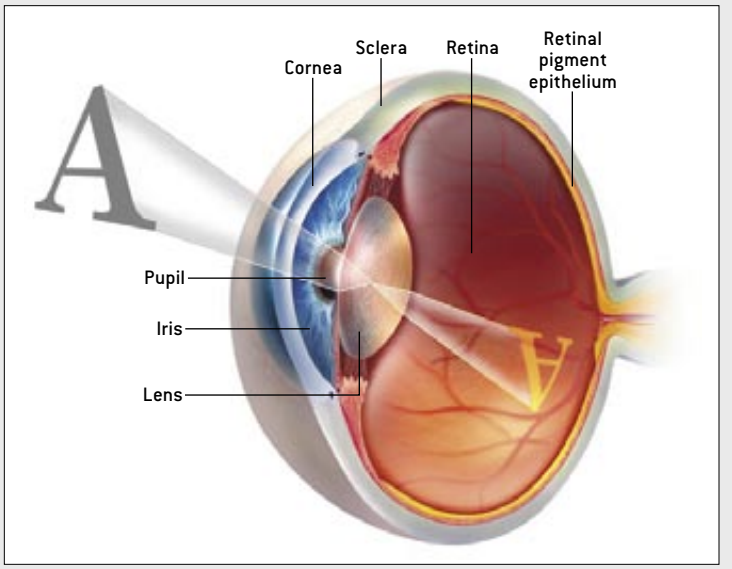
Even in the absence of such conditions, the inability to repair means that over the long term, small insults accumulate. Regular exposure to highly reactive molecules such as oxygen free radicals, or to ultraviolet radiation, or to years of elevated

Brown Eyes Blue

Knowing how the eye focuses light (*diagram*) explains not only how you see but why your eyes may be brown, hazel or blue—or red in a photograph. The iris blocks incoming light, leaving a neat hole—the pupil—through which light rays strike the lens and are focused onto the retina. The rays that hit the iris are scattered back. The shorter the light's wavelength the greater the scattering, so blue light is scattered more than red, giving the iris a "natural" blue color. (The same principle causes the sky and sea to appear blue.) Yet the iris also contains melanin—pigment molecules that absorb various wavelengths. A lot of melanin will absorb much of the light, making the iris appear dark brown. Less melanin leads to lighter browns and greens, and very little melanin allows blue to dominate.

The pupil appears black because a melanin-rich layer of cells just behind the retina—the retinal pigment epithelium—absorbs all light that the retina has not. This absorption prevents light from randomly scattering back to the retina's photoreceptors, which would blur vision. (The black lining of a camera serves the same purpose.) Because no light is emitted back through the pupil, it appears black.

Albinos cannot synthesize melanin; their retinal pigment epithelium does not absorb much light and thus causes poor vision and near-blindness in bright light. As light scatters back toward the pupil and iris, it illuminates blood vessels, making them appear pink or red. A similar effect can occur during flash photography of any person: the flash is so bright that the epithelium cannot absorb all the rays, and backscatter creates red-eye in the photograph. —*R.D.*



KEITH KASNOT

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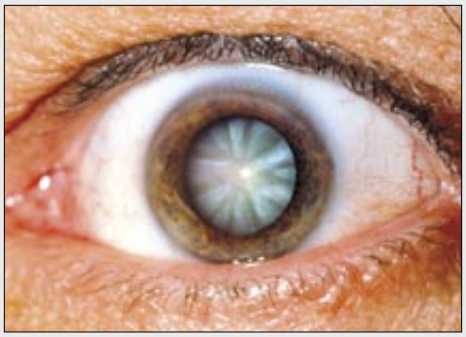
blood sugar from diabetes eventually leads to cataracts in many people—and to many cataract operations.

References to the removal of clouded lenses date back as early as 1800 B.C. to the Babylonian Code of Hammurabi. Ancient Egyptian texts and medieval European and Islamic writings describe detaching the lens from the ciliary muscle and pushing it down into the vitreous humor—the thick fluid in the back of the eye. Although this procedure removed the veil from the light path, it left no lens to focus rays. Patients could see only blurred images, as if their eyes were open underwater.

The application of special spectacles in the 17th and 18th centuries finally compensated for the lost focusing power. Today's artificial lenses eliminate any need for glasses. Doctors perform more than one million cataract operations annually in the U.S. alone. Fortunately, the procedure now has a success rate of nearly 100 percent and takes no more than 45 minutes. Still, approximately one third of patients return with after-cataracts, caused by undifferentiated cells—stem cells—that are inadvertently left behind during surgery. These cells start proliferating, but in contrast to their behavior during embryonic development, they form a disorganized mass that obscures vision and has to be surgically removed. In those developing countries that lack surgical resources, cataracts account for half of all cases of blindness. In India alone, cataracts blind an estimated 3.8 million people every year.

In addition to becoming vulnerable to cataracts, the aging lens tends to yellow. Proteins that absorb blue and green light slowly accumulate, blocking these rays from reaching the retina and thereby giving the lens a yellow or brownish appearance. Only reds, yellows and browns pass through, altering a person's view of the world [*see box on next page*].

How Cataracts Form



Cataracts in the lens blur the vision or blind millions of people every year. Lens cells contain a thick solution of large proteins called crystallins (*a*) in an ordered arrangement. Researchers have not yet determined why, but as crystallins accumulate damage, such as from ultraviolet light, oxidation or dehydration, they collapse into misfolded fibers (*b*). Then the misfolded proteins can aggregate into a tangled mass (*c*). The clumped mass blocks or distorts incoming light, creating a cloudy spot in a person's field of view (*photograph*). Elevated levels of misfolded proteins have been found in the brains of individuals with Alzheimer's or Parkinson's disease, prompting scientists to look deeper for common clues. —*R.D.*

Controlled Suicide

RECENTLY, scientists have done much more than marvel at the lens's qualities and fret over its age-related decline. They are finding that the process by which the lens systematically destroys its organelles may offer a marvelous opportunity to thwart some of humankind's most frustrating illnesses.

Like all cells, lens cells that arise from stem cells during early fetal development contain organelles. But as they differentiate, they demolish their organelles—and the rubble that remains—to become transparent. This may not seem problematic at first, but consider what happens when other cells encounter so much as a little damage to their DNA: they embark on an irreversible process called apoptosis, or programmed cell death. Destructive proteins released inside a cell chop up its DNA and key proteins, and the mitochondria shut down, depriving the cell of its energy source. The tattered cell breaks apart and dissolves. Ordinarily, damaged cells commit suicide to make room for new healthy cells—otherwise an organ with an accumulating number of damaged cells would not be able to function. In some cases, damaged cells kill themselves so they do not start proliferating and turn cancerous. Lens cells destroy the nucleus and every other organelle yet halt the process just before demolition is complete, leaving an intact outer membrane, an inner cytoskeleton of proteins and a thick crystallin plasma [*see box on pages 14 and 15*].

The ability to halt cellular suicide has come as quite a surprise. The scientific community had always viewed apoptosis as an unstoppable process. Yet some unknown mechanism in the lens controls the death machinery so it destroys only certain cell components while leaving others intact. Sev-

THE AUTHOR

RALF DAHM is a research group leader at the Center for Brain Research at the Medical University of Vienna. He has a Ph.D. in biochemistry from the University of Dundee in Scotland and oversaw a pan-European project to exploit zebra fish as a model for researching human development and diseases. He is co-editor of *Zebrafish: A Practical Approach* (Oxford University Press, 2002) and is author of a popular German-language science book about human embryonic development, stem cells and cloning. Dahm is also fascinated by how eye diseases change the way artists see and therefore render the world.

SCIENCE PHOTO LIBRARY (*photograph*); ALICE CHEN (*illustration*)

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eral years ago I, along with other lens specialists, began to suspect that a deliberate braking mechanism was involved. We showed that specific compartments of differentiating cells—the nucleus or mitochondria, say—succumb to the same destruction that occurs during the full apoptosis of mature cells. But other compartments such as the cytoskeleton are unaffected. The implication is that lens cells actually use the death machinery not to destroy themselves but to choreograph the differentiation process.

The next leap in thinking came quickly: a mechanism that could control apoptosis could alter the progression of diseases characterized by excessive cellular suicide, such as neurodegenerative disorders. To harness this power, researchers must find the signals—or blockers—that stop total destruction. Similarly, discovering what triggers lens cells to degrade their organelles could suggest new ways to induce cancer cells to commit suicide.

Pieces of evidence are accumulating. One theory advanced by Steven Bassnett of Washington University in St. Louis to explain the onset of apoptosis holds that during development, as new lens cells are formed around existing ones—like new layers around an onion core—the older internal cells become further removed from the surface, and the amount of oxygen that reaches them decreases. If the concentration drops below a threshold, the integrity of the mitochondria, which rely on an oxygen supply for energy production, might be compromised. Sensing this problem, the cell triggers the release of proapoptotic factors. This theory seems plausible in part because damaged mitochondria are known to initiate apoptosis in mature human cells. The

Painting through Old Eyes

French impressionist Claude Monet (1840–1926) reached the grand old age of 86. But advancing years seriously affected his eyesight. Cataracts clouded his vision, and the yellowing of the lenses in his eyes altered his color perception. His work over the final two decades of his life offers a vivid depiction of how these common impairments skew human sight.

The yellowing started first. Gradually, proteins that absorb the "cold colors" of violet, blue and, later, green accumulated in his lenses, blocking these light rays from reaching the retina. Red and yellow light still passed through, rendering Monet's world in increasingly warm tones.

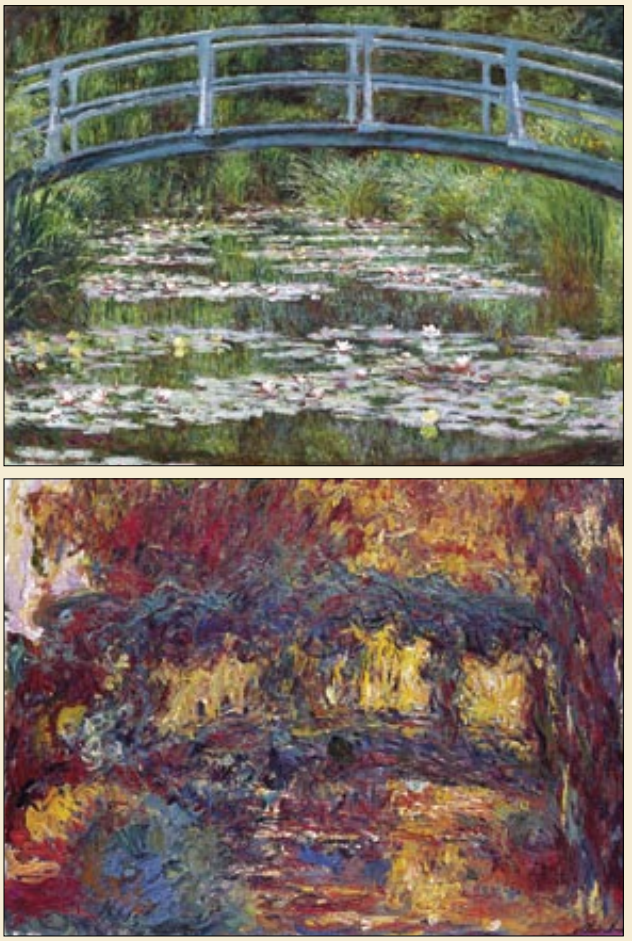
Cataracts then clouded his vision, forcing him to perceive his surroundings as if he were looking through frosted glass. Over time he had trouble discerning shapes, normal daylight became blinding, and in the late stages he could only differentiate between light and dark.

Monet first noticed that his eyes were changing during a trip to Venice in 1908. The 68-year-old painter had difficulty selecting his colors. In 1912 Monet's doctor diagnosed a cataract in each eye and recommended surgery, but the artist was afraid; in his time any operation was fraught with problems, and removing a cataract frequently ended an artist's career.

From that point on, however, Monet's works show fewer details. Yellows, reds and browns predominate. When he examined his later pictures, he was often seized by a towering rage and a desire to destroy them. In early 1922 he wrote that he was no longer able to create anything of beauty.

Later that year Monet's right eye could only detect light and the direction from which it came; his left eye could see only about 10 percent of what is considered normal. In January 1923, at the age of 83, he finally had cataract surgery to his right eye, but he complained that the glasses he had to wear thereafter made colors appear peculiar.

In 1925 he finally found suitable spectacles and was delighted. He wrote that he could see well again and would work hard. Alas, he died a year later. —*R.D.*



Claude Monet painted the Japanese footbridge in his Giverny garden near Paris in 1899 (*top*). The same scene, which he attempted to capture again between 1918 and 1924, shows that cataracts had blurred his vision and that the yellowing of his lenses had impaired his perception of blues and greens, leaving the artist in a world filled with murky reds and browns.

THE JAPANESE FOOTBRIDGE, BY CLAUDE MONET, GIFT OF VICTORIA NEBEKER COBERLY, IN MEMORY OF HER SON JOHN W. MUDD, AND WALTER H. AND LEONORE ANNENBERG, IMAGE © BOARD OF TRUSTEES, NATIONAL GALLERY OF ART, WASHINGTON, D.C. (*top*); MINNEAPOLIS INSTITUTE OF ARTS, BEQUEST OF PUTNAM DANA McMILLAN (*bottom*)

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death machinery is always there, ready to go. If the cell senses serious damage, it can release the block on the death machinery, and all hell breaks loose.

At the same time, Bassnett has proposed another potential cause of apoptosis: the lactic acid produced during the breakdown of glucose that occurs in differentiated lens cells. Mature cells in the lens's center lack mitochondria and produce energy by turning glucose into lactic acid. The acid forms a concentration gradient, along with a gradient in pH. Either gradient could start apoptosis.

Other triggers have attracted attention as well. In studies of lens cells in culture, Michael Wride, now at Cardiff University in Wales, and Esmond Sanders of the University of Alberta in Canada showed that tumor necrosis factor appears to promote the degradation of lens nuclei. Tumor necrosis factor is a messenger protein, or cytokine, that can act as a potent inducer of apoptosis in healthy cells and certain tumor cells. No one knows how this cytokine would work naturally in the lens, however.

Klaus van Leyen of Massachusetts General Hospital and his colleagues have uncovered clues to the molecules that respond to cell-death triggers. They found, for instance, that the enzyme 15-lipoxygenase can embed itself in the membranes of lens cell organelles and create holes in them. The holes allow proteases (enzymes that destroy proteins) to enter and destroy the organelles. Exactly what elicits the 15-lipoxygenase activity at the right time during lens cell differentiation remains unclear.

Research by this author and others has recently provided possible insights into the braking mechanism. In human, rat and mouse lenses, my colleagues and I found that a protein called galectin-3, which can bind to other molecules, is produced in lens cells that still have their organelles, but its synthesis is reduced when the organelles start to degrade. This activity pattern could control the apoptosis process, but we have no idea what triggers the shutoff of galectin-3. We began to look at galectin-3 because it is known to be involved in various biological functions related to cell proliferation, apoptosis and differentiation in other tissues.

Most recently, researchers in the laboratory of Shigekazu Nagata at Osaka University in Japan have identified a DNAse (an enzyme that cleaves DNA) that is essential for the degradation of DNA in lens cells. When this particular DNAse is missing in laboratory mice, they are born with cataracts; also, the apoptotic breakdown of the nuclei during the differentiation of lens cells does not seem to occur, whereas apoptosis appears to occur normally in all other cells. (Children can be born with cataracts if organelles are not degraded during fetal development, possibly as a result of a viral infection, such as rubella, in the mother.)

Of course, it is conceivable that rather than actively halting apoptosis in midstream, lens cells forestall death because some components simply are resistant to the molecules that effect self-destruction. For instance, proteins occurring only in the lens might be "invisible" to the killer enzymes that degrade the cytoskeletons of other cells. Alternatively, some evidence suggests that crystallins might form a protective barrier around certain proteins, preventing the enzymes from reaching those targets.

The death machinery is always there, ready to go. **If the cell senses serious damage, it can release** the block on the death machinery, and all hell breaks loose.

Swimming Zebras

AS WORK ADVANCES, a small fish could offer promising clues. The zebra fish is a terrific creature in which to study embryonic development. Its embryos have very few cells and are quite translucent early on, so experts can observe the formation of internal organs. Most organs develop incredibly fast—just 48 hours after eggs are laid. During day three, the fish hatch and start swimming around. Yet because zebra fish are vertebrates, the genetic control of their development is remarkably similar to that in humans.

Various groups have undertaken large-scale searches for mutant zebra fish, among them the laboratory of Nobel laureate Christiane Nüsslein-Volhard at the Max Planck Institute for Developmental Biology in Tübingen, Germany. Among the mutants we found were ones possessing lenses with intact organelles and others with lens cells that died completely. Some mutants had cataracts much like those in humans.

The labs are now looking to see if these mutants can provide new information about what starts and stops apoptosis. If so, the insights could advance medical research into ways to beat cell-death diseases. In the meantime, these studies should greatly improve our understanding of how and why cataracts form, which could lead to ways to slow their growth or prevent them altogether. That possibility alone keeps us focused. SA

MORE TO EXPLORE

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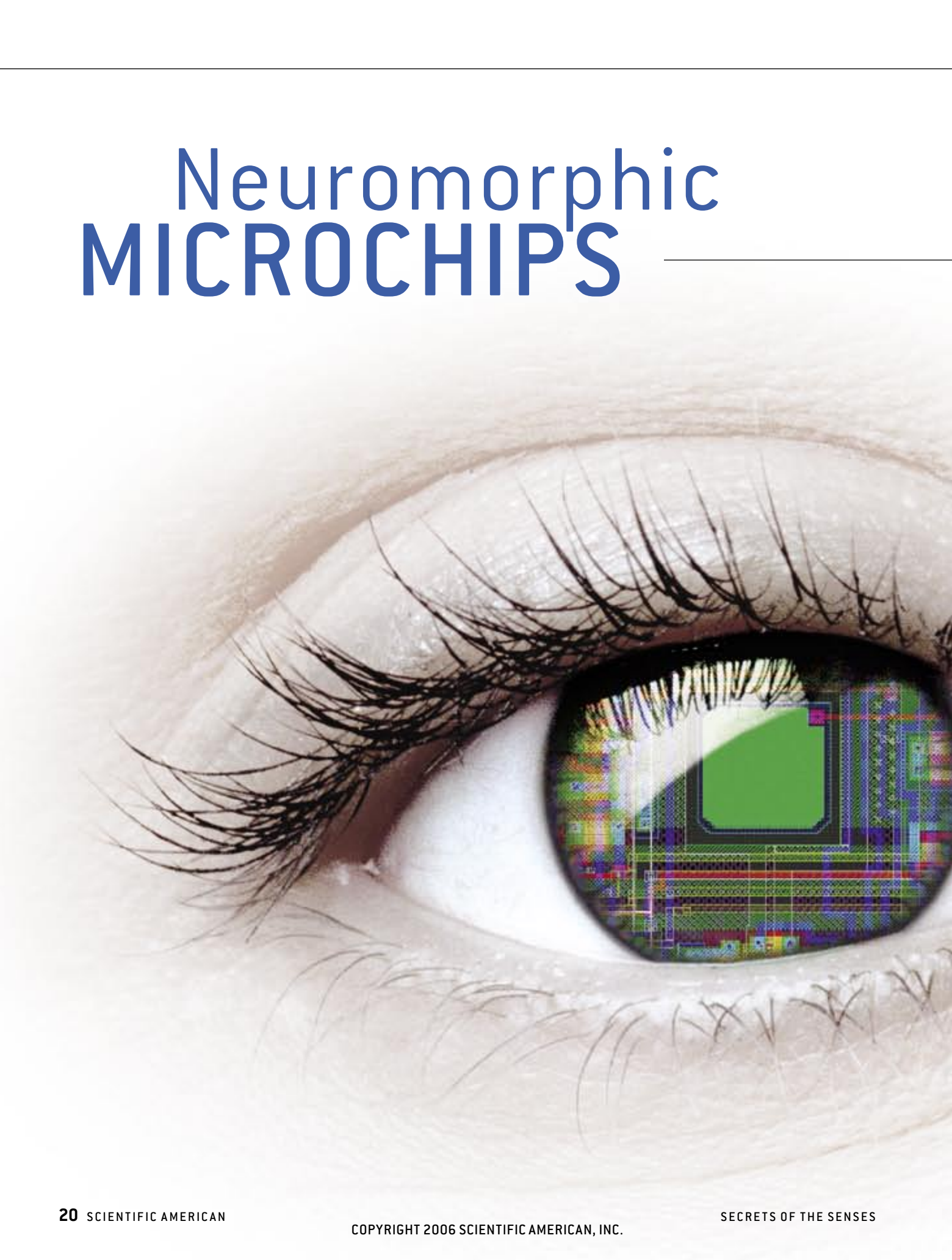
Neuromorphic MICROCHIPS



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Compact, efficient electronics based on the brain's neural system could yield implantable silicon retinas to restore vision, as well as robotic eyes and other smart sensors

BY KWABENA BOAHEN

When IBM's Deep Blue supercomputer edged out world chess champion Garry Kasparov during their celebrated match in 1997, it did so by means of sheer brute force. The machine evaluated some 200 million potential board moves a second, whereas its flesh-and-blood opponent considered only three each second, at most. But despite Deep Blue's victory, computers are no real competition for the human brain in areas such as vision, hearing, pattern recognition, and learning. Computers, for instance, cannot match our ability to recognize a friend from a distance merely by the way he walks. And when it comes to operational efficiency, there is no contest at all. A typical room-size supercomputer weighs approximately 1,000 times more, occupies 10,000 times more space and consumes a millionfold more power than does the cantaloupe-size lump of neural tissue that makes up the brain.

How does the brain—which transmits chemical signals between neurons in a relatively sluggish thousandth of a second—end up performing some tasks faster and more efficiently than the most powerful digital processors? The secret appears to reside in how the brain organizes its slow-acting electrical components.

The brain does not execute coded instructions; instead it activates links, or synapses, between neurons. Each such activation is equivalent to executing a digital instruction, so one can compare how many connections a brain activates every second with the number of instructions a computer executes during the same time. Synaptic activity is staggering: 10 quadrillion (10^{16}) neural connections a second. It would take a million Intel Pentium-powered computers to match that rate—plus a few hundred megawatts to juice them up.

Now a small but innovative community of engineers is making significant progress in copying neuronal organization and function. Researchers speak of having "morphed" the structure of neural connections into silicon circuits, creating neuromorphic microchips. If successful, this work could lead to implantable silicon retinas for the blind and sound processors for the deaf that last for 30 years on a single nine-volt battery or to low-cost, highly effective visual, audio, or olfactory recognition chips for robots and other smart machines [*see box on page 23*].

Our team at the University of Pennsylvania initially focused on morphing the retina—the half-millimeter-thick sheet of tissue that lines the

Implantable silicon retina, shown in this artist's conception, could emulate the eye's natural function, restoring vision for patients with certain types of blindness.

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Silicon retina senses the side-to-side head movements of University of Pennsylvania researcher Kareem Zaghloul. The four types of silicon ganglion cells on his Visio1 chip emulate real retinal cells' ability to preprocess visual information without huge amounts of computation. One class of cells responds to dark areas (*red*), whereas another reacts to light regions (*green*). A different set of cells tracks leading edges of objects (*yellow*) and trailing edges (*blue*). The gray-scale images, generated by decoding these messages, show what a blind person would see with neuromorphic retinal implants.

back of the eye. Comprising five specialized layers of neural cells, the retina "preprocesses" incoming visual images to extract useful information without the need for the brain to expend a great deal of effort. We chose the retina because that sensory system has been well documented by anatomists. We then progressed to morphing the developmental machinery that builds these biological circuits—a process we call metamorphing.

Overview/*Inspired by Nature*

- Today's computers can perform billions of operations per second, but they are still no match for even a young child when it comes to skills such as pattern recognition or visual processing. The human brain is also millions of times more energy-efficient and far more compact than a typical personal computer.
- Neuromorphic microchips, which take cues from neural structure, have already demonstrated impressive power reductions. Their efficiency may make it possible to develop fully implantable artificial retinas for people afflicted by certain types of blindness, as well as better electronic sensors.
- Someday neuromorphic chips could even replicate the self-growing connections the brain uses to achieve its amazing functional capabilities.

Neuromorphing the Retina

THE NEARLY ONE MILLION ganglion cells in the retina compare visual signals received from groups of half a dozen to several hundred photoreceptors, with each group interpreting what is happening in a small portion of the visual field. As features such as light intensity change in a given sector, each ganglion cell transmits pulses of electricity (known as spikes) along the optic nerve to the brain. Each cell fires in proportion to the relative change in light intensity over time or space—not to the absolute input level. So the nerve's sensitivity wanes with growing overall light intensity to accommodate, for example, the five-decade rise in the sky's light levels observed from predawn to high noon.

Misha A. Mahowald, soon after earning her undergraduate biology degree, and Carver Mead, the renowned microelectronics technologist, pioneered efforts to reproduce the retina in silicon at the California Institute of Technology. In their groundbreaking work, Mahowald and Mead reproduced the first three of the retina's five layers electronically. Other researchers, several of whom passed through Mead's Caltech laboratory (the author included), have morphed succeeding stages of the visual system as well as the auditory system. Kareem Zaghloul morphed all five layers of the retina in 2001 when he was a doctoral student in my lab, making it possible to emulate the visual messages that the ganglion cells, the retina's output neurons, send to the brain. His silicon retina chip, Visio1, replicates the responses of the retina's four major types of ganglion cells, which feed into and together make up 90 percent of the optic nerve [*see illustration at left*].

Zaghloul represented the electrical activity of each neuron in the eye's circuitry by an individual voltage output. The voltage controls the current that is conveyed by transistors connected between a given location in the circuit and other points, mimicking how the body modulates the responses of neural synapses. Light detected by electronic photosensors affects the voltage in that part of the circuit in a way that is analogous to how it affects a corresponding cell in the retina. And by tiling copies of this basic circuit on his chip, Zaghloul replicated the activity in the retina's five cell layers.

The chip emulates the manner in which voltage-activated ion channels cause ganglion cells (and neurons in the rest of the brain) to discharge spikes. To accomplish this, Zaghloul installed transistors that send current back onto the same location in the circuit. When this feedback current arrives, it increases the voltage further, which in turn recruits more feedback current and causes additional amplification. Once a certain initial level is reached, this regenerative effect accelerates, taking the voltage all the way to the highest level, resulting in a spike.

At 60 milliwatts, Zaghloul's neuromorphic chip uses one thousandth the electricity a PC does. With its low power needs, this silicon retina could pave the way for a total intraocular prosthesis—with camera, processor and stimulator all implanted inside the eye of a blind person who has retinitis pigmentosa or macular degeneration, diseases that damage

STONE [*eye photograph*]; KAREEM ZAGHLOUL [*retina layout*]; JEN CHRISTIANSEN [*photoillustration*] [*preceding pages*]; KAREEM ZAGHLOUL [*this page*]

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Neuromorphic Electronics Research Groups

Researchers seek to close the efficiency gap between electronic sensors and the body's neural networks with microchips that emulate the brain. This work focuses on small sensor systems that can be implanted in the body or installed in robots.

ORGANIZATION	INVESTIGATORS	PRINCIPAL OBJECTIVES
Stanford University	Kwabena Boahen	Silicon retina that re-creates optic nerve activity and self-configuring chips that emulate how the brain rewires itself
Johns Hopkins University	Andreas Andreou, Gert Cauwenberghs, Ralph Etienne-Cummings	Battery-powered speech recognizer, rhythm generator for locomotion and camera that extracts object features
ETH Zurich/ University of Zurich	Tobi Delbruck, Shih-Chii Liu, Giacomo Indiveri	Silicon retina and attention chip that automatically select salient regions in a scene
University of Edinburgh	Alan Murray, Alister Hamilton	Artificial noses and automatic odor recognition based on timing of signaling spikes
Georgia Institute of Technology	Steve DeWeerth, Paul Hasler	Coupled rhythm generators that coordinate a multisegmented robot
HKUST, Hong Kong	Bertram Shi	Binocular processor for depth perception and visual tracking
Massachusetts Institute of Technology	Rahul Sarpeshkar	Cochlea-based sound processor for implants for deaf patients
University of Maryland	Timothy Horiuchi	Sonar chip modeled on bat echolocation
University of Arizona	Charles Higgins	Motion-sensing chip based on fly vision

photoreceptors but spare the ganglion cells. Retinal prostheses currently being developed, for example, at the University of Southern California, provide what is called phosphene vision—recipients perceive the world as a grid of light spots, evoked by stimulating the ganglion cells with microelectrodes implanted inside the eye—and require a wearable computer to process images captured by a video camera attached to the patient's glasses. Because the microelectrode array is so small (fewer than 10 pixels by 10 pixels), the patient experiences tunnel vision—head movements are needed to scan scenes.

Alternatively, using the eye itself as the camera would solve the rubbernecking problem, and our chip's 3,600 ganglion-cell outputs should provide near-normal vision. Biocompatible encapsulation materials and stimulation interfaces need further refinement before a high-fidelity prosthesis becomes a reality, maybe by 2010. Better understanding of how various retinal cell types respond to stimulation and how they contribute to perception is also required. In the interim, such neuromorphic chips could find use as sensors in automotive or security applications or in robotic or factory automation systems.

Metamorphing Neural Connections

THE POWER SAVINGS we attained by morphing the retina were encouraging, a result that started me thinking about how the brain actually achieves high efficiency. Mead was prescient when he recognized two decades ago that even if computing managed to continue along the path of Moore's Law (which states that the number of transistors per square inch on integrated circuits doubles every 18 months), computers as we know them could not reach brainlike efficiency. But how could this be accomplished otherwise? The solution dawned on me nine years ago.

Efficient operation, I realized, comes from the degree to which the hardware is customized for the task at hand. Conventional computers do not allow such adjustments; the software is tailored instead. Today's computers use a few general-purpose tools for every job; software merely changes the order in which the tools are used. In contrast, customizing the hardware is something the brain and neuromorphic chips have in common—they are both programmed at the level of individual connections. They adapt the tool to the specific job. But how does the brain customize itself? If we could translate that mechanism into silicon—metamorphing—we could have our neuromorphic chips modify themselves in the same fashion. Thus, we would not need to painstakingly reverse-engineer the brain's circuits. I started investigating neural development, hoping to learn more about how the body produces exactly the tools it needs.

Building the brain's neural network—a trillion (10^{12}) neurons connected by 10 quadrillion (10^{16}) synapses—is a daunting task. Although human DNA contains the equivalent of a billion bits of information, that amount is not sufficient to specify where all those neurons should go and how they should connect. After employing its genetic information during early development, the brain customizes itself further through internal interactions among neurons and through external interactions with the world outside the body. In other words, sensory neurons wire themselves in response to sensory inputs. The overall rule that regulates this process is

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deceptively simple: neurons that fire together wire together. That is, out of all the signals that a neuron receives, it accepts those from neurons that are consistently active when it is active, and it ignores the rest.

To learn how one layer of neurons becomes wired to another, neuroscientists have studied the frog's retinotectal projection, which connects its retina to its tectum (the part of the midbrain that processes inputs from sensory organs). They have found that wiring one layer of neurons to another occurs in two stages. A newborn neuron extends projections ("arms") in a multilimbed arbor. The longest arm becomes the axon, the cell's output wire; the rest serve as dendrites, its input wires. The axon then continues to grow, towed by an amoeboid structure at its tip. This growth cone, as scientists call it, senses chemical gradients laid down by trailblazing precursors of neural communication signals, thus guiding the axon to the right street in the tectum's city of cells but not, so to speak, to the right house.

Narrowing the target down to the right house in the tectum requires a second step, but scientists do not understand this process in detail. It is well known, though, that neighboring retinal ganglion cells tend to fire together. This fact led me to speculate that an axon could find its retinal cell neighbors in the tectum by homing in on chemical scents released by active tectal neurons, because its neighbors were most likely at the source of this trail. Once the axon makes contact with the tectal neuron's dendritic arbor, a synapse forms between them and, voilà, the two neurons that fire together are wired together.

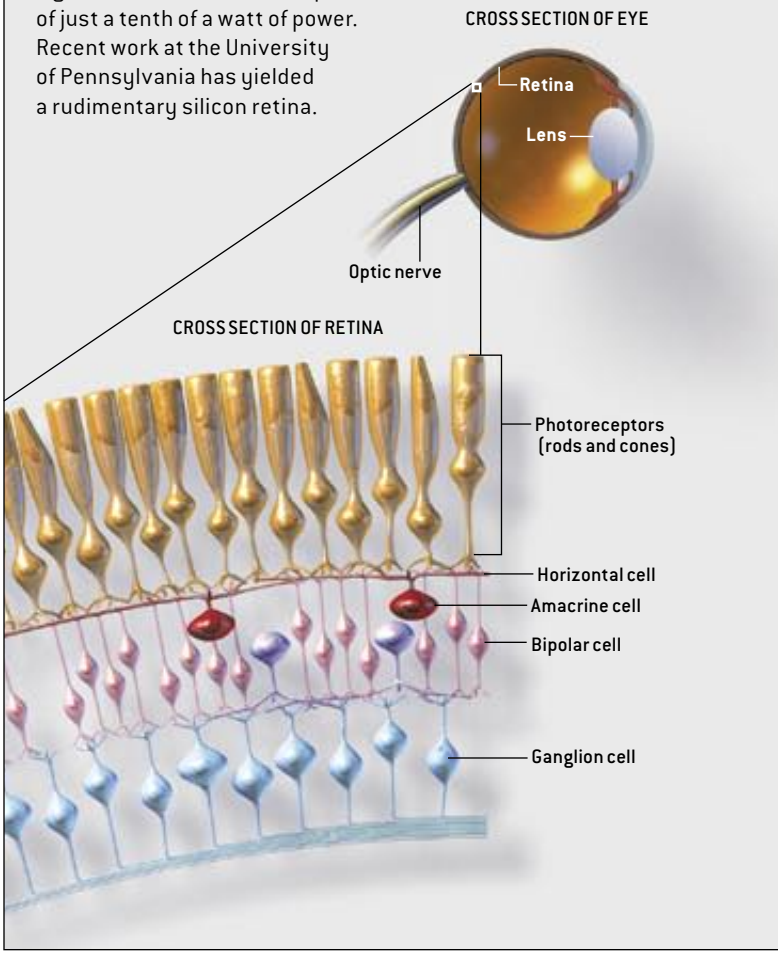
In 2001 Brian Taba, a doctoral student in my lab, built a chip modeled on this facet of the brain's developmental process. Because metal wires cannot be rerouted, he decided to reroute spikes instead. He took advantage of the fact that Zaghloul's Visio1 chip outputs a unique 13-bit address every time one of its 3,600 ganglion cells spikes. Transmitting addresses rather than spikes gets around the limited number of input/output pins that chips have. The addresses are decoded by the receiving chip, which re-creates the spike at the correct location in its silicon neuron mosaic. This technique produces a virtual bundle of axons running between corresponding locations in the two chips—a silicon optic nerve. If we substitute one address with another, we reroute a virtual axon belonging to one neuron (the original address) to another location (the substituted address). We can route these "softwires," as we call them, anywhere we want to by storing the substitutions in a database (a look-up table) and by using the original address to retrieve them [*see box on page 26*].

In Taba's artificial tectum chip, which he named Neurotrope1, softwires activate gradient-sensing circuits (silicon growth cones) as well as nearby silicon neurons, which are situated in the cells of a honeycomb lattice. When active, these silicon neurons release electrical charge into the lattice, which Taba designed to conduct charge like a transistor. Charge diffuses through the lattice much like the chemicals released by tectal cells do through neural tissue. The silicon growth cones sense this simulated diffusing "chemical" and drag their softwires up the gradient—toward the charge's silicon neuron source—by updating the look-up table. Because the charge must be released by the silicon neuron and sensed by the silicon growth cone simultaneously, the softwires end up connecting neurons that are active at the same time. Thus, Neurotrope1 wires together neurons that fire together, as would occur in a real growing axon.

Starting with scrambled wiring between the Visio1 chip and the Neurotrope1 chip, Taba successfully emulated the

Retinal Neurons and Neuromorphic Vision Chips

Biological sensory systems provide compact, energy-efficient models for neuromorphic electronic sensors. Engineers attempting to duplicate the retina in silicon face a tough challenge: the retina is only half a millimeter thick, weighs half a gram and consumes the equivalent of just a tenth of a watt of power. Recent work at the University of Pennsylvania has yielded a rudimentary silicon retina.



BRYAN CHRISTIE DESIGN; KAREEM ZAGHLOUL (*silicon retina*)

THE AUTHOR

KWABENA BOAHEN is a neuromorphic engineer and associate professor of bioengineering at Stanford University, where he moved in January after eight years on the faculty at the University of Pennsylvania. He left his native Ghana to pursue undergraduate studies in electrical and computer engineering at Johns Hopkins University in 1985 and became interested in neural networks soon thereafter. Boahen sees a certain elegance in neural systems that is missing in today's computers. He seeks to capture this sophistication in his silicon designs.

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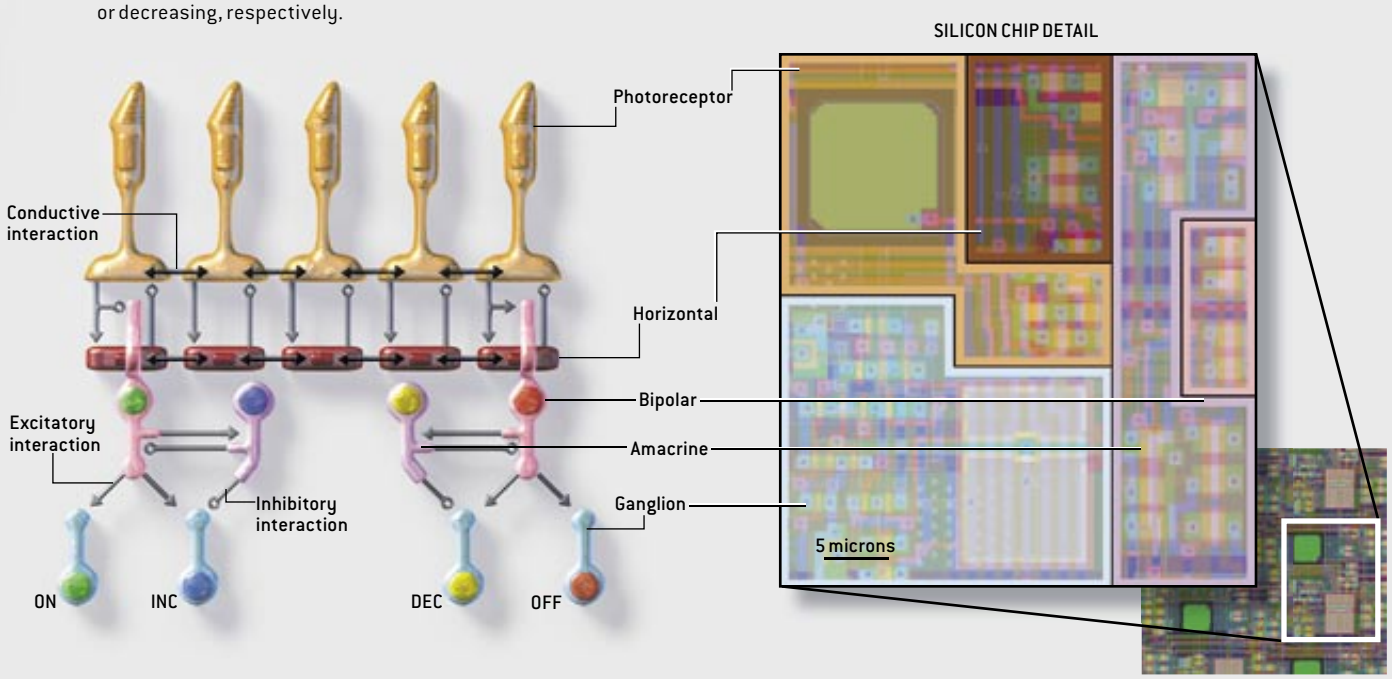
Biological Retina

The cells in the retina, which are interconnected, extract information from the visual field by engaging in a complex web of excitatory (*one-way arrows*), inhibitory (*circles on a stick*), and conductive or bidirectional (*two-way arrows*) signaling. This circuitry generates the selective responses of the four types of ganglion cells (*at bottom*) that make up 90 percent of the optic nerve's fibers, which convey visual information to the brain. On (*green*) and Off (*red*) ganglion cells elevate their firing (spike) rates when the local light intensity is brighter or darker than the surrounding region. Inc (*blue*) and Dec (*yellow*) ganglion cells spike when the intensity is increasing or decreasing, respectively.

Silicon Retina

Neuromorphic circuits emulate the complex interactions that occur among the various retinal cell types by replacing each cell's axons and dendrites (signal pathways) with metal wires and each synapse with a transistor. Permutations of this arrangement produce excitatory and inhibitory interactions that mimic similar communications among neurons. The transistors and the wires that connect them are laid out on silicon chips. Various regions of the chip surface perform the functions of the different cell layers. The large green squares are phototransistors, which transduce light into electricity.



tendency of neighboring retinal ganglion cells to fire together by activating patches of silicon ganglion cells at random. After stimulating several thousand patches, he observed a dramatic change in the softwiring between the chips. Neighboring artificial ganglion cells now connected to neurons in the silicon tectum that were twice as close as the initial connections. Because of noise and variability, however, the wiring was not perfect: terminals of neighboring cells in the silicon retina did not end up next to one another in the silicon tectum. We wondered how the elaborate wiring patterns thought to underlie biological cortical function arise—and whether we could get further tips from nature to refine our systems.

Cortical Maps

TO FIND OUT, we had to take a closer look at what neuroscience has learned about connections in the cortex, the brain region responsible for cognition. With an area 16 inches in diameter, the cortex folds like origami paper to fit inside the skull. On this amazing canvas, "maps" of the world outside are drawn during infancy. The best-studied example is what scientists call area V1 (the primary visual cortex), where visual messages from the optic nerve first enter the cortex. Not only are the length and width dimensions of an image mapped onto V1 but also the orientation of the edges of objects therein. As a result, neurons in V1 respond best to edges oriented at a particular angle—vertical lines, horizontal lines, and so forth. The same orientation preferences repeat every millimeter or so, thereby allowing the orientations of edges in different sectors of the visual scene to be detected.

Neurobiologists David H. Hubel and Torsten N. Wiesel, who shared a Nobel Prize in medicine for discovering the V1 map in the 1960s, proposed a wiring diagram for building a visual cortex—one that we found intimidating. According to their model, each cortical cell wires up to two groups of thalamic cells, which act as relays for retinal signals bound for the cortex. One group of thalamic cells should respond to the sensing of dark areas (which we emulate with Visio1's Off cells), whereas the other should react to the sensing of light (like our

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Visio1's On cells). To make a cortical cell prefer vertical edges, for instance, both groups of cells should be set to lie along a vertical line but should be displaced slightly so the Off cells lie just to the left of the On cells. In that way, a vertical edge of an object in the visual field will activate all the Off cells and all the On cells when it is in the correct position. A horizontal edge, on the other hand, will activate only half the cells in each group. Thus, the cortical cell will receive twice as much input when a vertical edge is present and respond more vigorously.

At first we were daunted by the detail these wiring patterns required. We had to connect each cell according to its orientation preference and then modify these wiring patterns systematically so that orientation preferences changed smoothly, with neighboring cells having similar preferences. As in the cortex, the same orientations would have to be repeated every millimeter, with those silicon cells wired to neighboring locations in the retina. Taba's growth cones certainly could not cope with this complexity. In late 2002 we searched for a way to escape this nightmare altogether. Finally, we found an answer in a five-decade-old experiment.

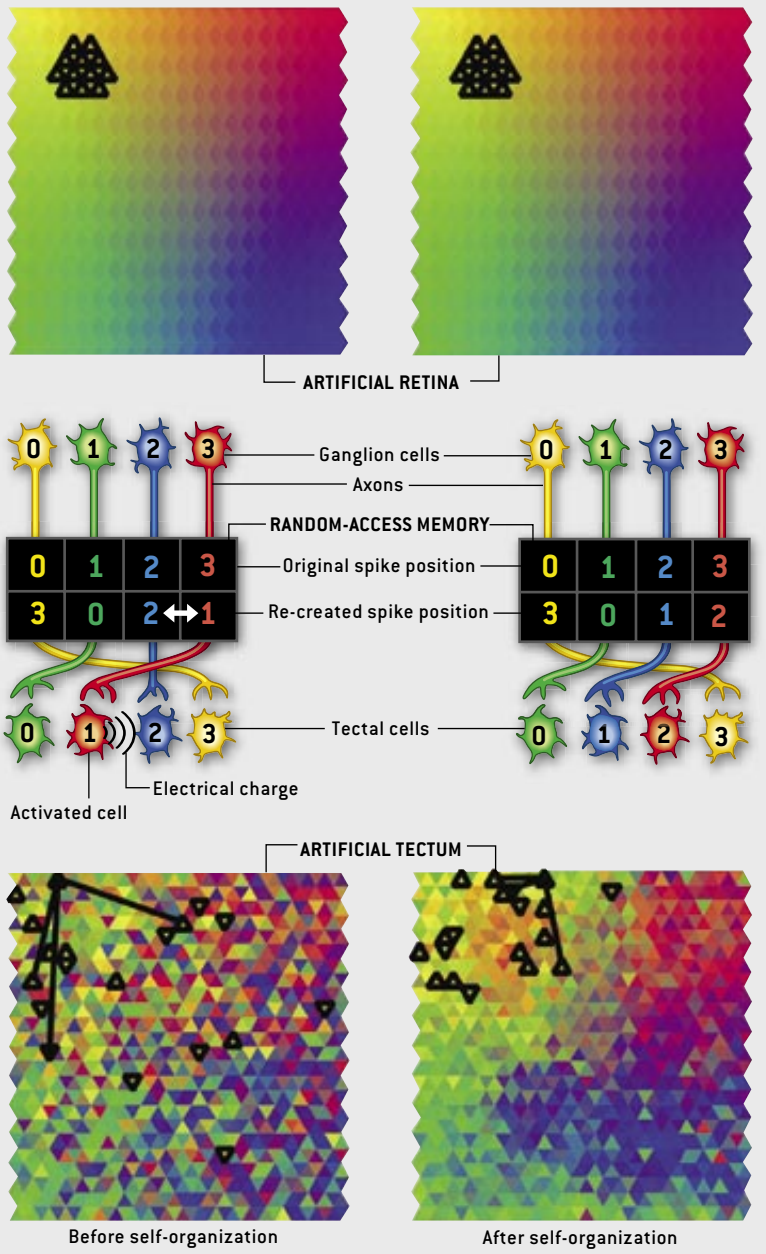
In the 1950s famed English computer scientist Alan Turing showed how ordered patterns such as a leopard's spots or a cow's dapples could arise spontaneously from random noise. We hoped we could use a similar technique to create neighbor-

Making Connections (Biological or Silicon)

In the early stages of the eye's development, ganglion cells in the retina project axons into a sensory center of the midbrain called the tectum. The retinal axons home in on chemical trails released by neighboring tectal cells that are activated at the same time, so neurons that fire together wire together. Ultimately, a map of the retinal sensors' spatial organization forms in the midbrain.

To emulate this process, University of Pennsylvania neuromorphic engineers use "softwires" to self-organize links between cells in their silicon retina chip, Visio1 (*top*), and those in their artificial tectum chip, Neurotrope1 (*bottom*). Electrical output pulses called spikes are "routed" from the artificial ganglion cells to the tectal cells using a random-access memory (RAM) chip (*middle*). The retinal chip supplies the address of the spiking silicon neuron, and the tectal chip re-creates that pulse at the corresponding location. In this example, the artificial tectum instructs the RAM to swap address entries 1 and 2. As a result, ganglion cell 2's axon terminus moves to tectal cell 1, bumping ganglion cell 3's axon from that location. The axons "sense" the gradient of electrical charge released by an activated silicon tectal cell, which helps to guide the connections.

After engineers repeatedly activated patches of neighboring silicon neurons in the artificial retina (*outlined triangles, top left*), the tectal cells' axon end points—which were initially widely distributed (*outlined triangles, bottom left*)—grew closer, yielding more uniform swaths on a colorized map (*bottom right*).



BRIAN TABA AND JEN CHRISTIANSEN

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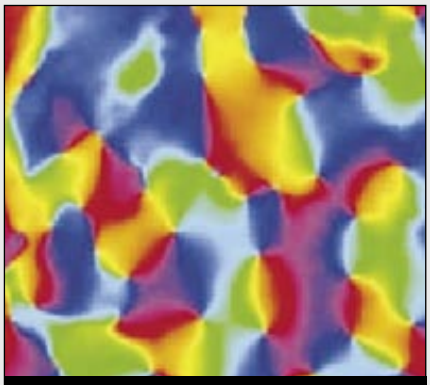
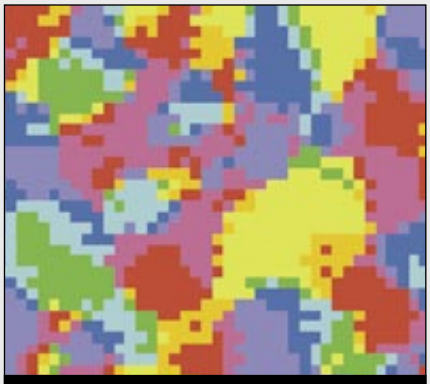
Orientation Preferences in the Brain and in Silicon

In both the visual cortex of a ferret (*left*) and a neuromorphic cortex chip (*right*), researchers have mapped the location of cells that respond preferentially to object edges of a certain orientation (*key, below*). In both maps, neighboring cells tend to have similiar orientation preferences, which shows that the cortex chip emulates the biological system.



Ferret cortex



Cortex chip

ing regions with similar orientation patterns for our chip. Turing's idea, which he tested by running simulations on one of the first electronic computers at the University of Manchester, was that modeled skin cells would secrete "black dye" or "bleach" indiscriminately. By introducing variations among the cells so that they produced slightly different amounts of dye and bleach, Turing generated spots, dapples and even zebralike stripes. These slight initial differences were magnified by blotting and bleaching to create all-or-nothing patterns. We wondered if this notion would work for cortical maps.

Building Brains in Silicon

FIVE YEARS AGO computational neuroscientist Misha Tsodyks and his colleagues at the Weizmann Institute of Science in Rehovot, Israel, demonstrated that, indeed, a similar process could generate cortexlike maps in software simulations. Paul Merolla, another doctoral student in my lab, took on the challenge of getting this self-organizing process to work in silicon. We knew that chemical dopants (impurities) introduced during the microfabrication process fell randomly, which introduced variations among otherwise identical transistors, so we felt this process could capture the randomness of gene expression in nature. That is putatively the source of variation of spot patterns from leopard to leopard and of orientation map patterns from person to person. Although the cells that create these patterns in nature express identical genes, they produce different amounts of the corresponding dye or ion channel proteins.

With this analogy in mind, Merolla designed a single silicon neuron and tiled it to create a mosaic with neuronlike excitatory and inhibitory connections among neighbors, which played the role of blotting and bleaching. When we fired up the chips in 2003, patterns of activity—akin to a leopard's spots—emerged. Different groups of cells became active when we presented edges with various orientations. By marking the locations of these different groups in different colors, we obtained orientation preference maps similar to those imaged in the V1 areas of ferret kits [*see box above*].

Having morphed the retina's five layers into silicon, our goal turned to doing the same to all six of the visual cortex's layers. We have taken a first step by morphing layer IV, the cortex's input layer, to obtain an orientation preference map in an immature form. At three millimeters, however, the cortex is five times thicker than the retina, and morphing all six cortical layers requires integrated circuits with many more transistors per unit area.

Chip fabricators today can cram a million transistors and 10 meters of wire onto a square millimeter of silicon. By the end of this decade, chip density will be just a factor of 10 shy of cortex tissue density; the cortex has 100 million synapses and three kilometers of axon per cubic millimeter.

Researchers will come close to matching the cortex in terms of sheer numbers of devices, but how will they handle a billion transistors on a square centimeter of silicon? Thousands of engineers would be required to design these high-density nanotechnology chips using standard methods. To date, a 100-fold rise in design engineers accompanied the 10,000-fold increase in the transistor count in Intel's processors. In comparison, a mere doubling of the number of genes in flies to that of humans enabled evolutionary forces to construct brains with 10 million times more neurons. More sophisticated developmental processes made possible the increased complexity by elaborating on a relatively simple recipe. In the same way, morphing neural development processes instead of simply morphing neural circuitry holds great promise for handling complexity in the nanoelectronic systems of the future. SA

MORE TO EXPLORE

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The author's Web site: **www.stanford.edu/group/boahen**

MARCOS FRANK (*ferret*); PAUL MEROLLA (*chip*)

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Listening with two ears

Studies of barn owls offer insight into just how the brain combines acoustic signals from two sides of the head into a single spatial perception

BY MASAKAZU KONISHI

Why do people have two ears? We can, after all, make sense of sounds quite well with a single ear. One task, however, requires input from both organs: pinpointing the exact direction from which a sound, such as the cry of a baby or the growl of a dog, is emanating. In a process called binaural fusion, the brain compares information received from each ear and then translates the differences into a unified perception of a single sound issuing from a specific region of space.

Extensive research has shown that the spatial cues extracted by the human brain are differences in the arrival time and the intensity, or force, of sound waves reaching the ears from a given spot. Differences arise because of the distance between the ears. When a sound comes from a point directly in front of us, the waves reach both ears at the same time and exert equal force on the receptive surfaces that relay information to the brain. But if a sound emanates from, say, left of center, the waves will reach the right ear slightly after the left. They will also be somewhat less intense at the right because, as they travel to the far ear, some fraction of the waves will be absorbed or deflected by the head.

The brain's use of disparities in timing and intensity becomes especially obvious when tones are delivered separately to each ear through a headset. Instead of perceiving two distinct signals, we hear one signal—a phantom—originating from somewhere inside or outside the head. If the stimuli fed to the ears are equally intense (equally loud) and are conveyed simultaneously, we perceive one sound arising from the middle of the head. If the volume is lowered in just one ear or if delivery to that ear is delayed, the source seems to move in the direction of the opposite ear.

This much has long been known. What is less clear is how the brain manages to detect variances in timing and intensity and how it combines the resulting information into a unified spatial perception. My colleagues and I at the California Institute of Technology have been exploring this question for more than 25 years by studying the behavior and brain of the barn owl (*Tyto alba*). We have uncovered almost every step of the computational process in these animals. (The only other sensory vertebrate system that is as completely defined belongs to a fish.) We find that the owl brain combines aural signals relating to location not all at once but through an amazing series of steps. Information about timing and intensity is processed separately in parallel pathways that converge only late in those pathways. It is highly probable that humans and other mammals achieve binaural fusion in much the same manner.

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Barn owl pinpoints prey in the dark by listening. It determines the appropriate trajectory in which to fly by comparing differences in the timing and the intensity of sounds reaching its two ears.

STEPHEN DALTON *Minden Pictures*

Turning Heads

I FIRST THOUGHT of examining the neural basis of sound location in owls in 1963, when I heard Roger S. Payne, now at the Whale Conservation Institute in Lincoln, Mass., report that the barn owl can catch a mouse readily in darkness, solely by relying on acoustic cues. I had recently earned a doctorate in zoology and wanted to know more about how animals identify the position of a sound source, but I had yet to choose a species to study. Three years later, at Princeton University, I observed the exquisite aural abilities of barn owls for myself after I obtained three of them from a bird-watcher. When I watched one of the owls through an infrared-sensitive video camera in a totally dark room, I was impressed by the speed and accuracy with which it turned its head toward a noise. I concluded that the head-turning response might help uncover whether such animals use binaural fusion in locating sound. If they did, studies of their brain could help elucidate how such fusion is accomplished.

As I had anticipated, the head-turning response did prove extremely useful to me and my postdoctoral fellows, particularly after I established a laboratory at Caltech in 1975. In some of our earliest research there, Eric I. Knudsen, now at Stanford University, and I obtained indirect evidence that barn owls, like humans, must merge information from the two ears to locate a sound. When one ear was plugged, the animals turned the head in response to noise from a loudspeaker, but they did not center on the speaker.

In the early 1980s Andrew Moiseff and I additionally showed that the barn owl extracts directional information from disparities in the timing and the intensity of signals reaching the two ears—technically called interaural time differences and interaural intensity differences. As part of that effort, we measured the differences that arose as we moved a speaker across the surface of an imaginary globe around an owl's head. Microphones we had placed in the ears relayed the signals reaching each ear to a device that measured arrival time and volume. When we eased the speaker from the midline of the face (zero angle) 90 degrees to the left or right, the difference in arrival time at the two ears increased systematically. Those results resembled the findings of human studies.

In contrast to human findings, the difference in intensity did not vary appreciably as the speaker was moved horizontally. But it did increase as the speaker was moved up or down from eye level—at least when the sound included waves of frequencies higher than three kilohertz, or 3,000 cycles per second. Payne, who had seen the same intensity changes in ear-

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lier studies, has attributed them, apparently correctly, to an asymmetry in the placement of the owl's ears. The left ear is higher than eye level but points downward, whereas the right ear is lower but points upward. The net result is that the left ear is more sensitive to sounds coming from below, and the right is more sensitive to sounds from above.

Satisfied that arrival time and intensity often differ for the two ears, we could go on to determine whether the owl actually uses specific combinations of disparities in locating sound sources. We intended to put a standard headset on tame animals and to convey a noise separately to each ear, varying the difference in delivery time or volume, or both. We would then see whether particular combinations of time and intensity differences caused the animals to turn the head reliably in specific directions. Unfortunately, we did not receive cooperation from our subjects. When we tried to affix the earphones, each owl we approached shook its head and backed off. We managed to proceed only after we acquired tiny earphones that could be inserted into the owls' ear canal.

We also had to devise a way to measure the direction of head turning, determining both the horizontal and vertical components of the response to each set of stimuli. We solved the problem mainly by applying the search-coil technique that Gary G. Blasdel, now at Northwestern University's Feinberg School of Medicine, had designed a few years earlier. We fit two small coils of copper wire, arranged perpendicularly to each other, on an owl's head. We positioned the owl between two big coils carrying electric current. As the head moved, the large coils induced currents in the small ones. Variations in the flow of current in the smaller coils revealed both the horizontal and vertical angles of the head turning.

Sure enough, the owl responded rapidly to signals from the earphones, just as if it had heard noise arising from outside the head. When the sound in one ear preceded that in the other ear, the head turned in the direction of the leading ear. More precisely, if we held the volume constant but issued the sound to one ear slightly before the other ear, the owl turned its head mostly in the horizontal direction. The longer we delayed delivering the sound to the second ear, the further the head turned.

Similarly, if we varied intensity but held timing constant, the owl tended to move its head up or down. If we issued sounds so that both the delivery time and the intensity of signals to the left ear differed from those of the right, the owl moved its head horizontally and vertically. Indeed, combinations of interaural timing and intensity differences that mimicked the combinations generated from a speaker at particular sites caused the animal to turn toward exactly those same sites. We could therefore be confident that the owl brain does fuse timing and intensity data to determine the horizontal and vertical coordinates of a sound source. The process by which barn owls calculate distance is less clear.

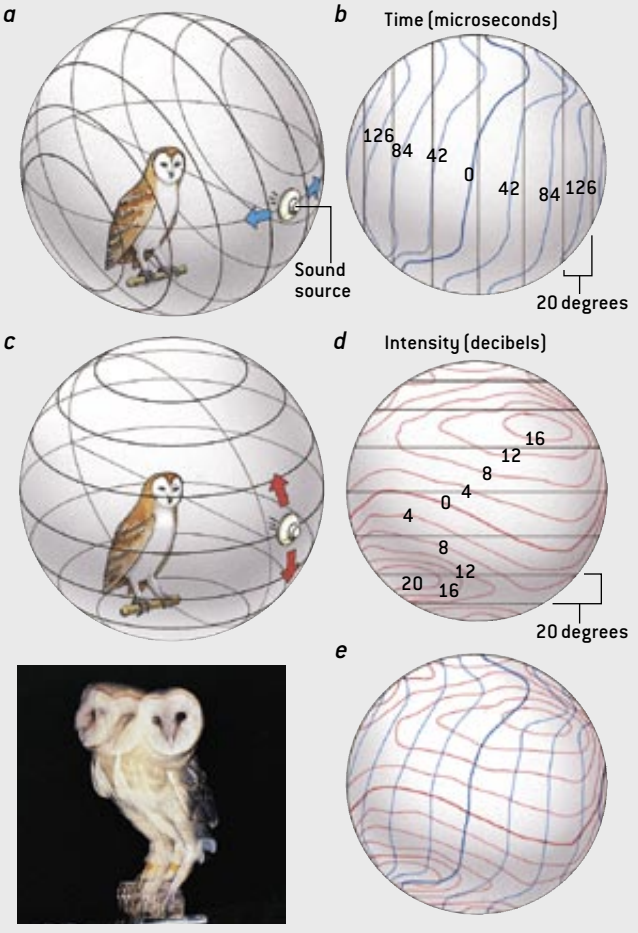
Fields in Space

TO LEARN HOW the brain carries out binaural fusion, we had to examine the brain itself. Our research plan built on work Knudsen and I had completed several years earlier. We had identified cells that are now known to be critical to sound location. Called space-specific neurons, they react only to acoustic stimuli originating from specific receptive fields, or restricted areas in space [*see box on opposite page*]. These neurons reside in a region of the brain called the external nucleus, which is situated within the auditory area of the midbrain (the equivalent of the mammalian inferior colliculus). Collectively, the space-specific neurons in the left external nucleus form a map of primarily the right side of auditory space (the broad region in space from which sounds can be detected),

Coordinates of Sound

Differences in timing and intensity at which a sound reaches an owl's two ears vary as the source of the sound moves along the surface of an imaginary globe around the owl's head. Differences in timing locate the sound in the horizontal plane (*a*); the difference increases 42 microseconds every 20 degrees a sound source moves (*b*).

Differences in intensity locate the sound vertically (*c*). Sound from above eye level is more intense in the right ear, by the decibel levels shown (*d*); from below eye level, it is more intense in the left ear. Differences vary with frequency; they were measured for six kilohertz in this case. Combining the two graphs (*e*) defines each location in space. When an owl is exposed to a particular pair of differences, it quickly turns its head in a predictable direction (*photograph*).



JANA BRENNING (*illustrations*); MICHAEL S. BRAINARD (*data for b and d*) AND ERIC I. KNUDSEN *Stanford University* (*photograph*)

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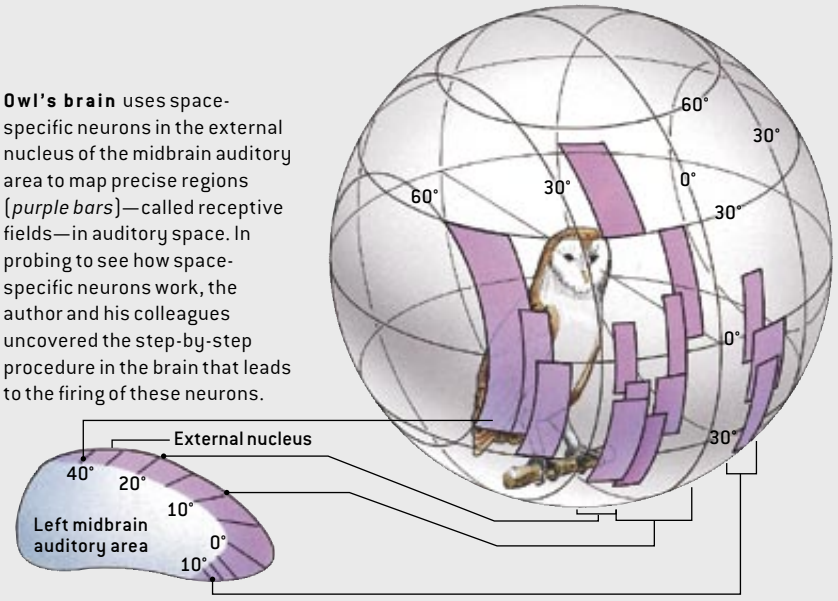
Owl's brain uses space-specific neurons in the external nucleus of the midbrain auditory area to map precise regions (*purple bars*)—called receptive fields—in auditory space. In probing to see how space-specific neurons work, the author and his colleagues uncovered the step-by-step procedure in the brain that leads to the firing of these neurons.



and those of the right external nucleus form a map of primarily the left half of auditory space, although there is some overlap.

We identified the space-specific cells by resting a microelectrode, which resembles a sewing needle, on single neurons in the brain of an anesthetized animal. As we held the electrode in place, we maneuvered a speaker across the surface of our imaginary globe around the owl's head. Certain neurons fired impulses only if the noise emanated from a particular receptive field. For instance, in an owl facing forward, one space-specific neuron might respond only if a speaker were placed within a receptive field extending roughly 20 degrees to the left of the owl's line of sight and some 15 degrees above or below it. A different neuron would fire when the speaker was transferred elsewhere on the globe.

How did these neurons obtain directional information? Did they process the relevant cues themselves? Or were the cues extracted and combined to some extent at one or more lower way stations (relay centers) in the brain [*see box on pages 34 and 35*], after which the results were simply fed upward?

Moiseff and I intended to answer these questions by carrying out experiments in which we would deliver sounds through earphones. But first we had to be certain that signals able to excite particular space-specific neurons truly mimicked the interaural time and intensity differences that caused the neurons to fire under more natural conditions—namely, when a sound emanated from a spot in the neuron's receptive field. A series of tests gave us the encouragement we needed. In these studies, we issued sounds through the earphones and monitored the response of individual neurons by again holding a microelectrode on or near the cells. As we hoped, we found that cells responded to specific combinations of signals. Further, the sets of timing and intensity differences that triggered strong firing by space-specific neurons corresponded exactly to the combinations that caused an owl to turn its head toward a spot in the neuron's receptive field. This congruence affirmed that our proposed approach was sensible.

In our initial efforts to trace the steps by which the brain circuitry accomplishes binaural fusion, Moiseff and I tried to find neurons sensitive to interaural timing or intensity differences in the way stations that relay signals from the auditory nerve up to the midbrain. These preliminary investigations, completed in 1983, suggested that certain stations are sensitive only to timing cues, whereas others are sensitive solely to intensity cues. The brain, it seemed, functioned like a parallel computer, processing information about timing and intensity through separate circuits.

Parallel Processing

SUCH CLUES led us to seek further evidence of parallel processing. Joined by Terry T. Takahashi, now at the University of Oregon, we began by examining the functioning of the lowest way stations in the brain—the cochlear nuclei. Each cerebral hemisphere has two: the magnocellular nucleus and the angular nucleus. In owls, as in other birds, each fiber of the auditory nerve—that is, each signal-conveying axon projecting from a neuron in the ear—divides into two branches after leaving the ear. One branch enters the magnocellular nucleus; the other enters the angular nucleus.

We wondered how the space-specific neurons would behave if we prevented nerve cells from firing in one of the two cochlear nuclei. We therefore injected a minute amount of a local anesthetic into either the magnocellular or angular nucleus. The results were dramatic: the drug in the magnocellular nucleus altered the response of space-specific neurons to interaural time differences without affecting the response to intensity differences. The converse occurred when the angular nucleus received the drug. Evidently, timing and intensity are indeed processed separately, at least at the lowest way stations of the brain; the magnocellular neurons convey timing data, and the angular neurons convey intensity data.

These exciting results spurred me to ask Takahashi to map the trajectories of the neurons that connect way stations in the auditory system. His work eventually revealed that two separate pathways extend from the cochlear nuclei to the midbrain. The anatomical evidence, then, added further support to the parallel-processing model.

While Takahashi was conducting his mapping research, W. E. Sullivan and I explored the ways magnocellular and angular nuclei extract timing and intensity information from signals arriving from the auditory nerve. To understand our discoveries, one must be aware that most sounds in nature

THE AUTHOR

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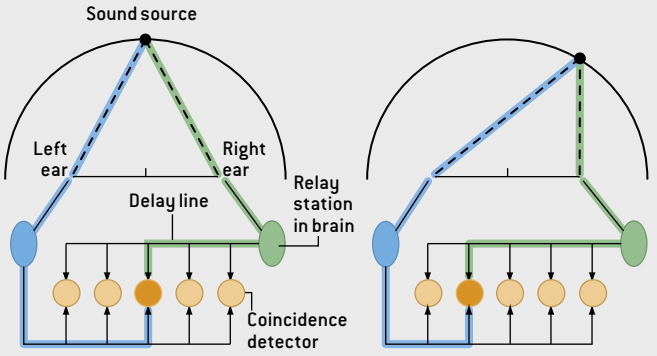
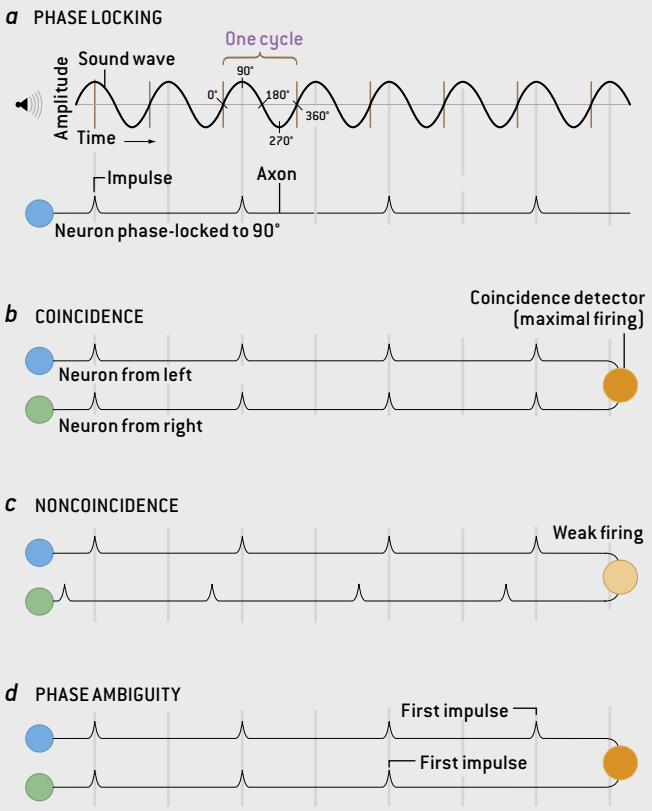
Detecting Differences

Model circuit for detection of interaural time differences was suggested in 1948. The coincidence detectors receive inputs from both ears. They fire only when impulses from the two sides arrive simultaneously through fibers that serve as delay lines. The detector that responds (*darkly colored circle*) changes as a sound source moves from directly in front of an individual (*left*) to the side (*right*). The owl brain operates in much the way the model proposed.



Sound wave of a single frequency causes neurons sensitive to it to fire trains of impulses at a particular phase angle (*a*). Coincidence detectors in the owl's brain fire most strongly when impulses generated at the same phase angle reach the detectors simultaneously (*far right in b*). Detectors can also fire, but more weakly, when impulse trains reaching them are slightly asynchronous (*c*). In what is called phase ambiguity, peak firing can occur if a sound to one ear is delayed or advanced by a full cycle from another delivery time that yields coincidence (*d*).



are made up of several waves, each having a different frequency. When the waves reach a receptive surface in the ear, called the basilar membrane, the membrane begins to vibrate, but not uniformly. Different parts of the membrane vibrate maximally in response to particular frequencies. In turn, neurons that are connected to the maximally vibrating areas (and thus are "tuned" to specific frequencies) become excited. These neurons propagate impulses along the auditory nerve to the brain.

We and others find that the intensity of a sound wave of a given frequency is conveyed to the brain from the ear by the firing rate of auditory neurons tuned to that frequency. This much makes intuitive sense. Our next result is less obvious. Neurons of the auditory nerve also exhibit what is called phase locking: they fire at characteristic points, or phase angles, along the sound wave [*see bottom illustration in box at left*]. That is, a neuron tuned to one frequency will tend to fire, for example, when the wave is at baseline (zero degrees), although it does not necessarily fire every time the wave reaches that position. A neuron tuned to a different frequency will tend to fire at a different phase angle, such as when a wave is cresting (at the point called 90 degrees, which is a quarter of the way through a full 360-degree wave cycle), or reaches some other specific point. In both ears, impulses produced by neurons tuned to the same frequency will lock to the same phase angle. But, depending on when the signals reach the ears, the train of impulses generated in one ear may be delayed relative to the impulse train generated in the opposite ear.

It turns out that cells of the magnocellular nucleus exhibit phase locking. But they are insensitive to intensity; changes in the volume of a tone do not affect the rate of firing. In contrast, few angular neurons show phase locking, although they respond distinctly to changes in intensity. These and other results indicate that the owl depends on trains of phase-locked impulses relayed from the magnocellular nucleus for measuring interaural time differences, and the animal relies on the rate of impulses fired by the angular nucleus for gauging interaural intensity differences. Overall, then, our analyses of the lowest way stations of the brain established that the cochlear nuclei serve as filters that pass along information about timing or intensity, but not both.

Way Stations in the Brain

WE THEN PROCEEDED to explore higher regions, pursuing how the brain handles timing data in particular. Other studies, which will be discussed, addressed intensity. We learned that when phase-locked impulses induced by sound waves of a single frequency (a pure tone) leave the magnocellular nucleus on each side of the brain, they travel to a second way station: the laminar nucleus. Impulses from each ear are transmitted to the nucleus on both the opposite and the same side of the head. The laminar nucleus is, therefore, the first place where the information from both ears comes together in one place.

JASON KÜFFER

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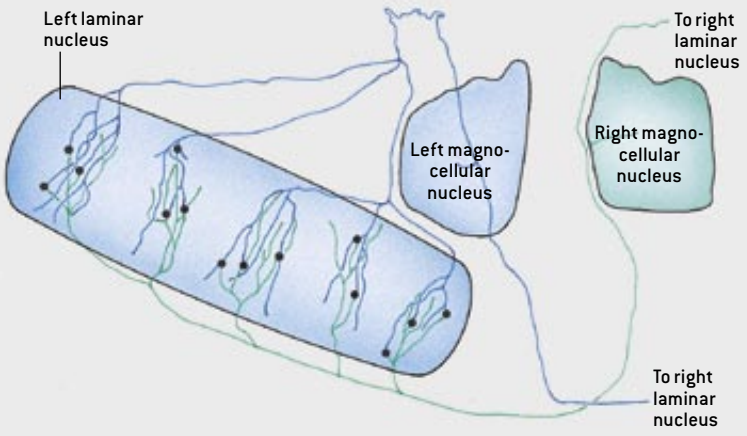

Fibers from the magnocellular nucleus serve as delay lines, and neurons in the laminar nucleus act as coincidence detectors in the owl's brain. When impulses traveling through the left (*blue*) and right (*green*) fibers reach laminar neurons (*black dots*) simultaneously, the neurons fire strongly.

The general problem of how the brain combines timing data has been a subject of speculation for decades. Lloyd A. Jeffress put forth a reasonable model in 1948, while spending a sabbatical leave at Caltech. Jeffress proposed that the nerve fibers carrying time-related signals from the ears (called delay lines) vary in how rapidly they deliver signals to way stations in the brain. They ultimately converge at neurons (known as coincidence detectors) that fire only when impulses from the two sides arrive simultaneously.

Signals reaching the ears at different times would attain coincidence—arrive at coincidence detectors in unison—if the sum of a sound wave's transit time to an ear and the travel time of impulses emanating from that ear to a coincidence detector were equal for the two sides of the head. Consider a sound that reached the left ear five microseconds before it reached the right ear. Impulses from the two ears would meet simultaneously at a coincidence detector in, say, the right hemisphere if the delay lines from the left ear (the near ear) prolonged the transit time of impulses from that ear to a coincidence detector by five microseconds over the time it would take impulses to traverse fibers from the right ear [*see top illustration in box on opposite page*].

Since 1948, physiological studies examining neuronal firing in dogs and cats and anatomical studies of chicken brains have suggested that the brain does in fact measure interaural time differences by means of delay lines and coincidence detection. In 1986 Catherine E. Carr, now at the University of Maryland, and I demonstrated in the barn owl that nerve fibers from magnocellular neurons serve as delay lines and neurons of the laminar nucleus serve as coincidence detectors.

Firing Squad

BUT THE OWL'S detection circuit, like those of other mammals that have been examined, differs somewhat from the Jeffress model. Neurons of the laminar nucleus respond most strongly to coincidence brought about by particular time differences. Yet they also respond, albeit less strongly, to signals that miss perfect coincidence. The number of impulses declines gradually as the interaural time difference increases or decreases from the value that produces coincidence—that is, until the waves reaching one ear are 180 degrees (a full half cycle) out of phase from the position that would bring about coincidence. At that point, firing virtually ceases. (The neurons also respond, at an intermediate level, to signals delivered to just one ear.)

In a way, then, coincidence detectors, by virtue of the delay lines feeding them, can be said to be maximally sensitive to specific time differences. They are not, however, totally selective as to when they produce a peak response. They can be induced to fire with rising strength as the phase difference increases beyond 180 degrees from the value that produces coincidence. When the displacement reaches a full 360 degrees, the arrival time of sound waves at one ear is delayed by the time it takes for a sound wave to complete a full cycle. In that situation, and at every 360-degree difference, coincidence detectors will repeatedly be hit by a series of synchronous impulses and will fire maximally. Thus, the same cell can react to more than one time difference. This phenomenon is called phase ambiguity.

After a coincidence detector in the laminar nucleus on one side of the brain determines the interaural time difference produced by a sound of a given frequency, it simply passes the result upward to higher stations, including to the core region of the midbrain auditory area on the opposite side of the head. Consequently, the higher areas inherit from the laminar nucleus not only selectivity for frequency and interaural time differences but also phase ambiguity. The information in the core, in turn, is passed to a surrounding area—known as the shell of the midbrain auditory area—on the reverse side of the brain, where it is finally combined with information about intensity.

The Intensity Pathway

MY COLLEAGUES AND I understand less about the operation of the intensity pathway that converges with the time pathway in the shell. But we have made good progress. Unlike the magnocellular nucleus, which projects up only one stage, to the laminar nucleus, the intensity-detecting angular nucleus projects directly to many higher stations (except the external nucleus). Among them is the posterior lateral lemniscal nucleus.

The posterior lateral lemniscal nucleus receives inhibitory signals from its counterpart on the other side of the head and gets excitatory signals from the angular nucleus on that side as well. The balance between excitatory and inhibitory signals determines the rate at which the lemniscal neurons fire in response to intensity differences in sound between the ears. Geoffrey A. Manley and Christine Köppl of the Technical University of Munich showed in my laboratory that the

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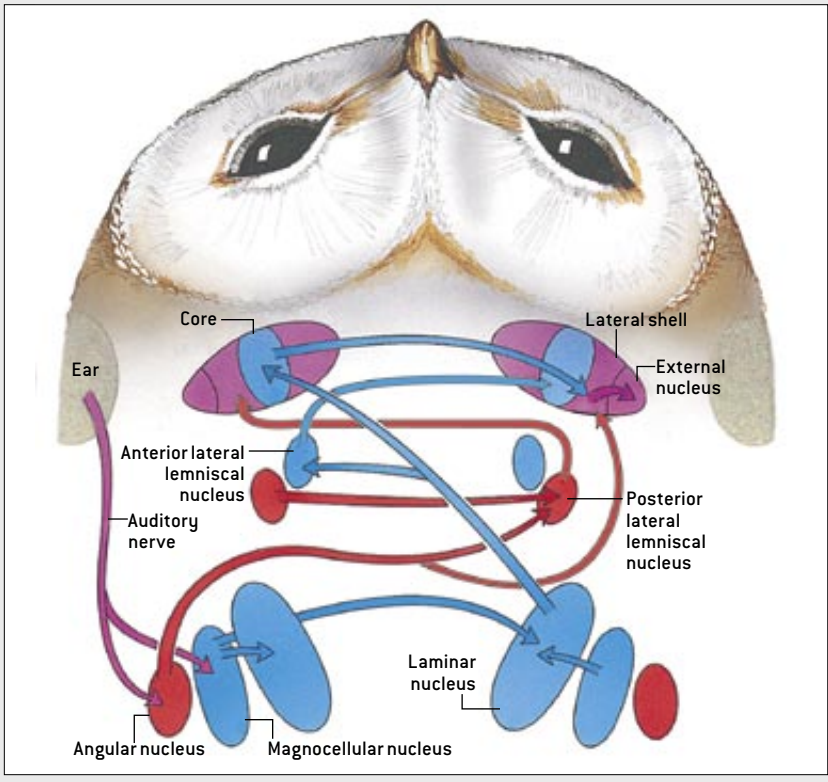
The Auditory Circuit

Parallel pathways in the barn owl's brain separately process the timing (*blue*) and the intensity (*red*) of sounds reaching the ears (*diagram and flow chart*). The simplified diagram depicts the pathways only for the left ear except where input from the right ear joins that pathway; brain structures are not drawn to scale. Processing begins as the magnocellular nucleus separates out information about time and as the angular nucleus extracts information about intensity from signals delivered by the auditory nerve. The time pathway goes to the laminar nucleus, which receives input from both the right and the left magnocellular nuclei. Neurons of the laminar nucleus are connected to two higher stations: the anterior lateral lemniscal nucleus and the core of the midbrain auditory area. Meanwhile information about intensity travels from the angular nucleus to the posterior lateral lemniscal nucleus, where information from the two ears comes together. The time and intensity pathways finally join in the lateral shell of the midbrain auditory area. They project from there to the external nucleus, which houses the space-specific neurons and is the final station in processing the acoustic cues for locating a sound. If viewed in terms of an algorithm (*far right*), a set of step-by-step procedures for solving a problem, these neurons are at the top of the hierarchy: they represent the final results of all computations that take place in the network.



strength of the inhibition declines systematically from dorsal to ventral within the nucleus. This finding indicates that neurons selective for different intensity disparities form an orderly array within the nucleus. To the barn owl, sounds that are louder in the left ear indicate "down," and sounds that are louder in the right ear indicate "up." The posterior lemniscal nucleus is, therefore, the first site that computes and maps sound source elevation.

The next higher station is the lateral shell of the midbrain auditory area; neurons from the posterior lemniscal nucleus on each side of the brain send signals to the shell in the opposite hemispheres. In the shell, most neurons respond strongly to both interaural intensity and interaural timing differences generated by sounds within a narrow range of frequencies. This station does not provide the owl with sufficient information to ensure accurate sound location, however, because phase ambiguity persists.

The ambiguity disappears only at the level of the external nucleus, home of the space-specific neurons. These neurons are broadly tuned to frequency, receiving timing and intensity data from many frequency channels. This convergence supplies the input needed for the brain to select the correct coordinates of a sound source. The selectivity of space-specific neurons, then, results from the parallel processing of time and intensity data and from the combination of the results in the shell and in the external nucleus itself.

We have not yet resolved the number of space-specific neurons that must fire in order for an owl to turn its head toward a sound source. Nevertheless, we know that individual neurons can carry the needed spatial data. This fact belies the view of some researchers that single neurons cannot represent such complex information and that perceptions arise only when whole groups of cells that reveal nothing on their own fire impulses collectively in a particular pattern.

Neural Algorithms

TOGETHER our neurological explorations have elucidated much of the algorithm, or step-by-step protocol, by which the owl brain achieves binaural fusion. Presumably, we humans follow essentially the same algorithm (although some of the processing stations might differ). Recall, for example, that several lines of evidence suggest mammals rely on delay lines and coincidence detection in locating sounds.

We can extrapolate even further. The only other neural algorithm for a sensory task that has been deciphered in equal detail is one followed by electricity-emitting fish of the genus *Eigenmannia*. Walter F. Heiligenberg of the University of California, San Diego, and his associates worked out the rules enabling members of this species to determine whether their electric waves are of higher or lower frequency than those of other *Eigenmannia* in the immediate vicinity. (In response, a fish might alter the frequency of the wave it emits.) *Eigenmannia* rely on parallel pathways to process separate sensory information. Also, relevant information is processed in steps; the parallel pathways converge at a high station; and neurons at the top of the hierarchy respond selectively to

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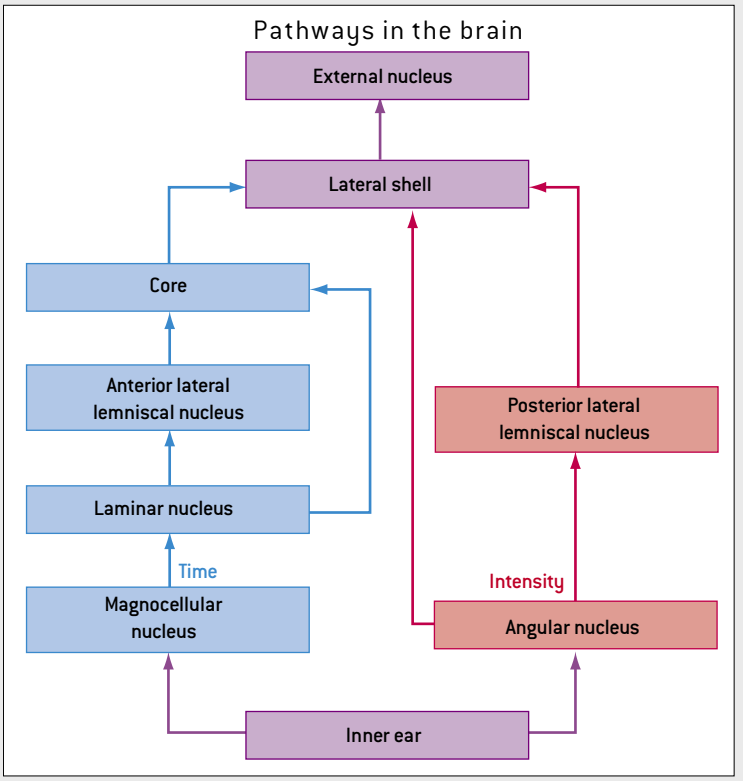

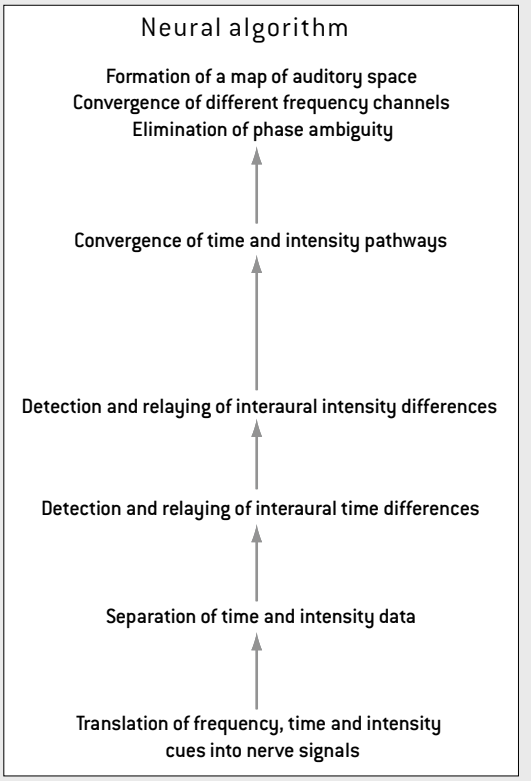
Neural algorithm
Formation of a map of auditory space
Convergence of different frequency channels
Elimination of phase ambiguity
Convergence of time and intensity pathways
Detection and relaying of interaural intensity differences
Detection and relaying of interaural time differences
Separation of time and intensity data
Translation of frequency, time and intensity cues into nerve signals

precise combinations of cues. The fish algorithm is thus remarkably similar to that of the barn owl, even though the problems that are solved, the sensory systems involved, the sites of processing in the brain and the species are different. The similarities suggest that brains follow certain general rules for information processing that are common to different sensory systems and species.

Carver A. Mead, here at Caltech, thinks the owl algorithm may also teach something to designers of analog silicon chips, otherwise known as VLSI (Very Large Scale Integrated) circuits. In 1988 he and John Lazzaro, then his graduate student, constructed an "owl chip" that reproduces the steps through which the barn owl measures interaural time differences. The model, about 73 square millimeters in area, contains only 64 auditory nerve fibers in each ear (many fewer than truly exist) and some 21,000 delay lines. (It also has 200,000 transistors, mainly to regulate the delay lines.) Even in its pared-down version, the electronic nervous system takes up much more space and energy than does the biological system. Historically, engineers have constructed chips according to principles drawn from electronics, physics and chemistry. The economy of the biological circuit suggests that natural principles may help engineers build analog chips that consume less energy and take up less space than usual.

My laboratory's research into the owl brain is by no means finished. Beyond filling in some of the gaps in our knowledge of binaural fusion, we hope to begin addressing other problems. For example, the late Alvin M. Liberman of Haskins Laboratories in New Haven, Conn., proposed that the human brain processes speech sounds separately from nonspeech sounds. By the same token, we can ask whether the owl separately processes signals for sound location and other acoustic information. Some brain stations that participate in spatial orientation may also take part in other sensory activities, such as making owls selectively attuned to the calls of mates and chicks. How does the owl, using one set of neurons, sort out the algorithms for different sensory tasks? By solving such riddles for the owl, we should begin to answer some of the big questions that relate to more complex brains and, perhaps, to all brains. SA

MORE TO EXPLORE

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Listen: Making Sense of Sound. Exhibition opens October 21, 2006, at San Francisco's Exploratorium. **www.exploratorium.edu/listen**

JOHNNY JOHNSON

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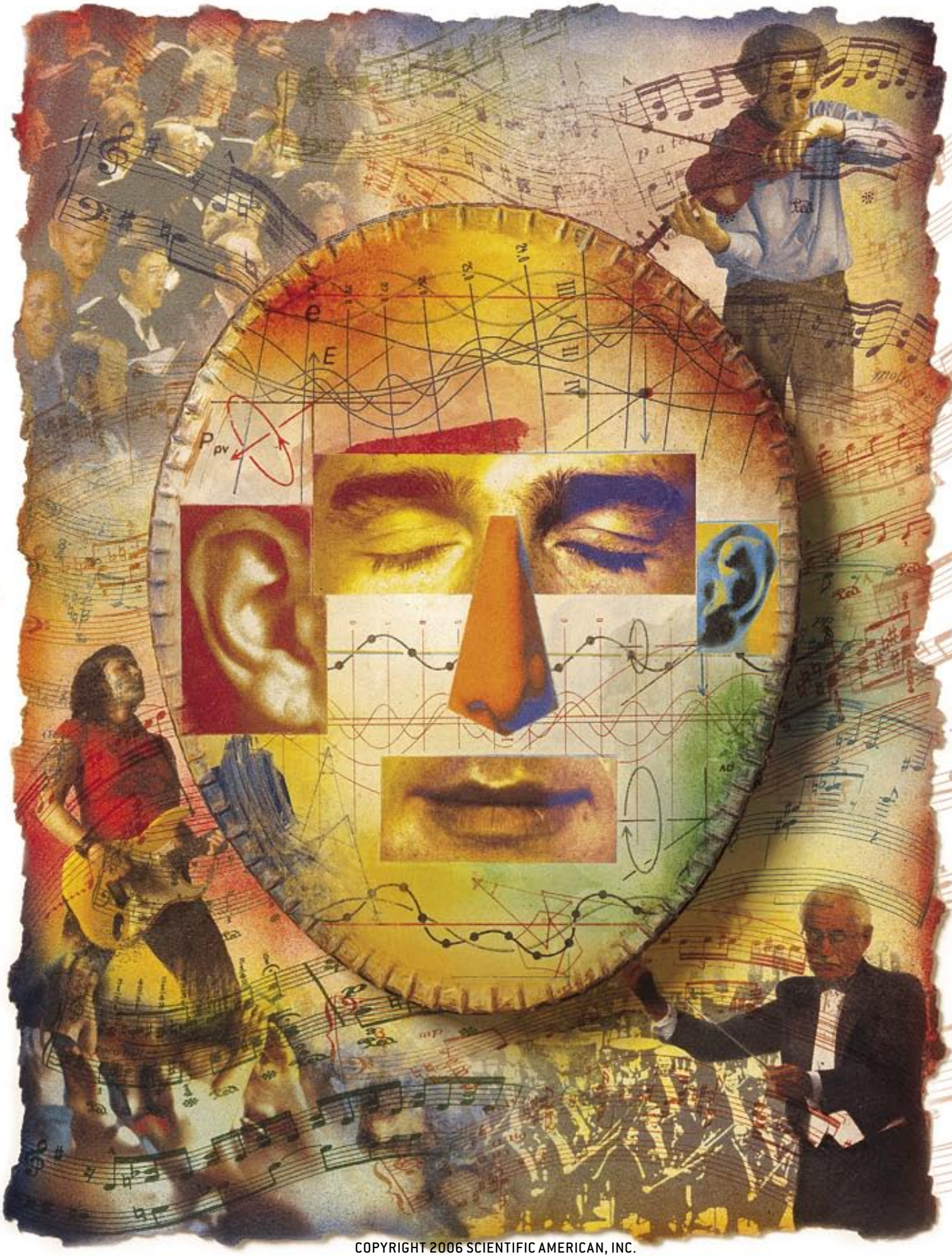

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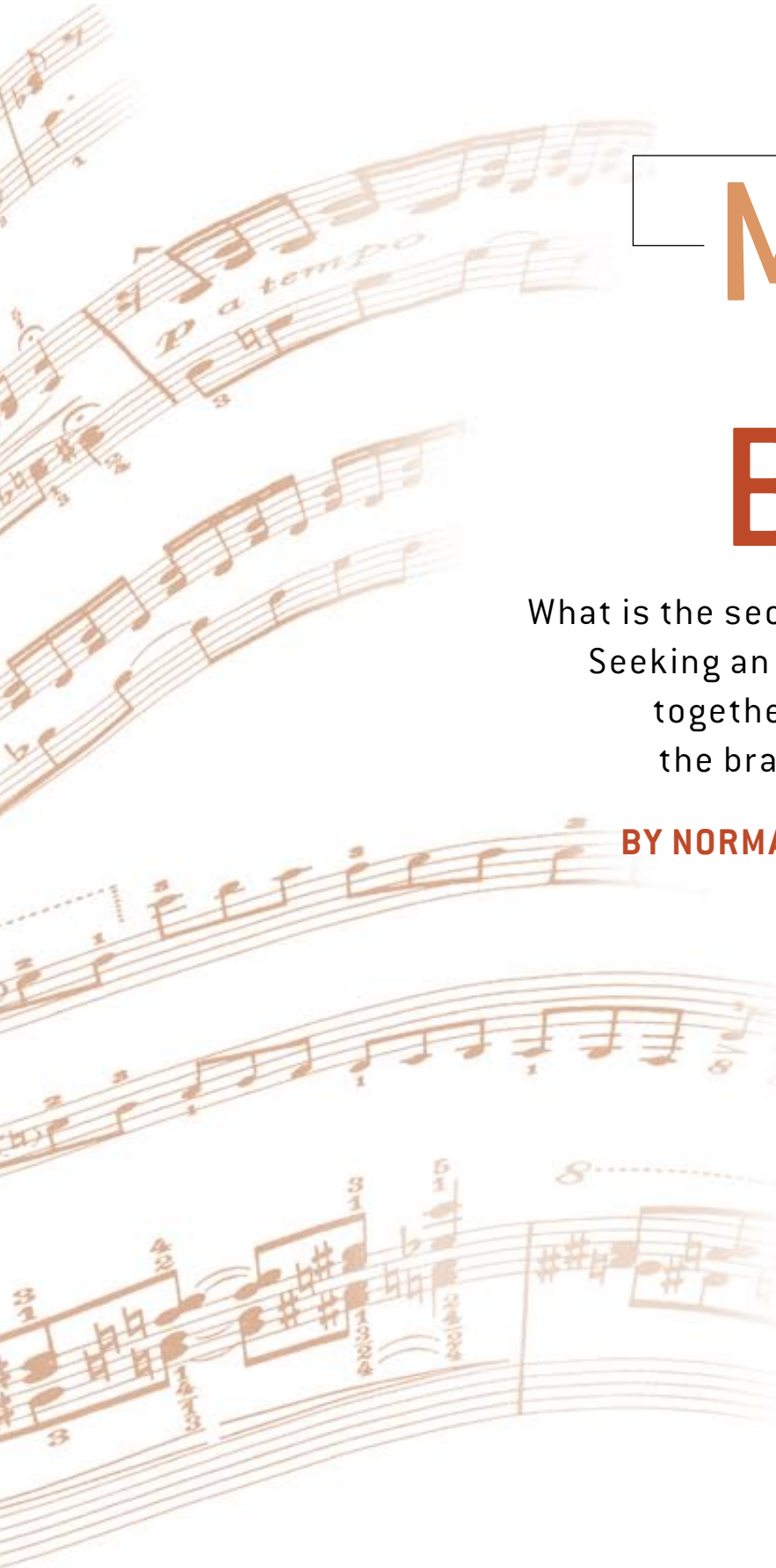

MUSIC AND THE BRAIN

What is the secret of music's strange power? Seeking an answer, scientists are piecing together a picture of what happens in the brains of listeners and musicians

BY NORMAN M. WEINBERGER

Music surrounds us—and we wouldn't have it any other way. An exhilarating orchestral crescendo can bring tears to our eyes and send shivers down our spines. Background swells add emotive punch to movies and TV shows. Organists at ballgames bring us together, cheering, to our feet. Parents croon soothingly to infants.

And our fondness has deep roots: we have been making music since the dawn of culture. More than 30,000 years ago early humans were already playing bone flutes, percussive instruments and jaw harps—and all known societies throughout the world have had music. Indeed, our appreciation appears to be innate. Infants as young as two months will turn toward consonant, or pleasant, sounds and away from dissonant ones [*see box on page 42*]. And the same kinds of pleasure centers light up in a person's brain whether he or she is getting chills listening to a symphony's denouement or eating chocolate or having sex or taking cocaine.

Therein lies an intriguing biological mystery: Why is music—universally beloved and uniquely powerful in its ability to wring emotions—so pervasive and important to us? Could its emergence have enhanced human survival somehow, such as by aiding courtship,

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as Geoffrey F. Miller of the University of New Mexico has proposed? Or, as suggested by Robin I. M. Dunbar of the University of Liverpool in England, did it originally help us by promoting social cohesion in groups that had grown too large for grooming? On the other hand, to use the words of Harvard University's Steven Pinker, is music just "auditory cheesecake"—a happy accident of evolution that happens to tickle the brain's fancy?

Neuroscientists don't yet have the ultimate answers. But in recent years we have begun to gain a firmer understanding of where and how music is processed in the brain, which should lay a foundation for answering evolutionary questions. Collectively, studies of patients with brain injuries and imaging of healthy individuals have unexpectedly uncovered no specialized brain "center" for music. Rather music engages many areas distributed throughout the brain, including those that are usually involved in other kinds of cognition. The active areas vary with the person's individual experiences and musical training. The ear has the fewest sensory cells of any sensory organ—3,500 inner hair cells occupy the ear versus 100 million photoreceptors in the eye. Yet our mental response to music is remarkably adaptable; even a little study can "retune" the way the brain handles musical inputs.

Why is music—universally beloved and uniquely powerful in its ability to wring emotions—so pervasive and important to us?

Inner Songs

UNTIL THE ADVENT of modern imaging techniques, scientists gleaned insights about the brain's inner musical workings mainly by studying patients—including famous composers—who had experienced brain deficits as a result of injury, stroke or other ailments. For example, in 1933 French composer Maurice Ravel began to exhibit symptoms of what might have been focal cerebral degeneration, a disorder in which discrete areas of brain tissue atrophy. His conceptual abilities remained intact—he could still hear and remember his old compositions and play scales. But he could not write music. Speaking of his proposed opera *Jeanne d'Arc,* Ravel confided to a friend, "… this opera is here, in my head. I hear it, but I will never write it. It's over. I can no longer write my music." Ravel died four years later, following an unsuccessful neurosurgical procedure. The case lent credence to the idea that the brain might not have a specific center for music.

The experience of another composer additionally suggested that music and speech were processed independently. After suffering a stroke in 1953, Vissarion Shebalin, a Russian composer, could no longer talk or understand speech, yet he retained the ability to write music until his death 10 years later. Thus, the supposition of independent processing appears to be true, although more recent work has yielded a more nuanced understanding, relating to two of the features that music and language share: both are a means of communication, and each has a syntax, a set of rules that govern the proper combination of elements (notes and words, respectively). According to Aniruddh D. Patel of the Neurosciences Institute in San Diego, imaging findings suggest that a region in the frontal lobe enables proper construction of the syntax of both music and language, whereas other parts of the brain handle related aspects of language and music processing.

Imaging studies have also given us a fairly fine-grained picture of the brain's responses to music. These results make the most sense when placed in the context of how the ear conveys sounds in general to the brain [*see box on opposite page*]. Like other sensory systems, the one for hearing is arranged hierarchically, consisting of a string of neural processing stations from the ear to the highest level, the auditory cortex. The processing of sounds, such as musical tones, begins with the inner ear (cochlea), which sorts complex sounds produced by, say, a violin, into their constituent elementary frequencies. The cochlea then transmits this information along separately tuned fibers of the auditory nerve as trains of neural discharges. Eventually these trains reach the auditory cortex in the temporal lobe. Different cells in the auditory system of the brain respond best to certain frequencies; neighboring cells have overlapping tuning curves so that there are no gaps. Indeed, because neighboring cells are tuned to similar frequencies, the auditory cortex forms a "frequency map" across its surface [*see box on page 41*].

The response to music per se, though, is more complicated. Music consists of a sequence of tones, and perception of it depends on grasping the relations between sounds. Many

Overview/*The Musical Brain*

- Music has been ubiquitous in human societies throughout the world since the dawn of culture. Appreciation for music appears to be innate; infants as young as two months will turn toward pleasant sounds.
- Many different regions of the brain respond to the perceptual and emotional aspects of music, and the brain alters itself to react more strongly to musical sounds that become meaningful to an individual.
- Scientists who study how music is processed in the brain are laying the groundwork to understand the underlying reasons for music's power and importance to humans.

JOHN STEWART (*preceding pages*)

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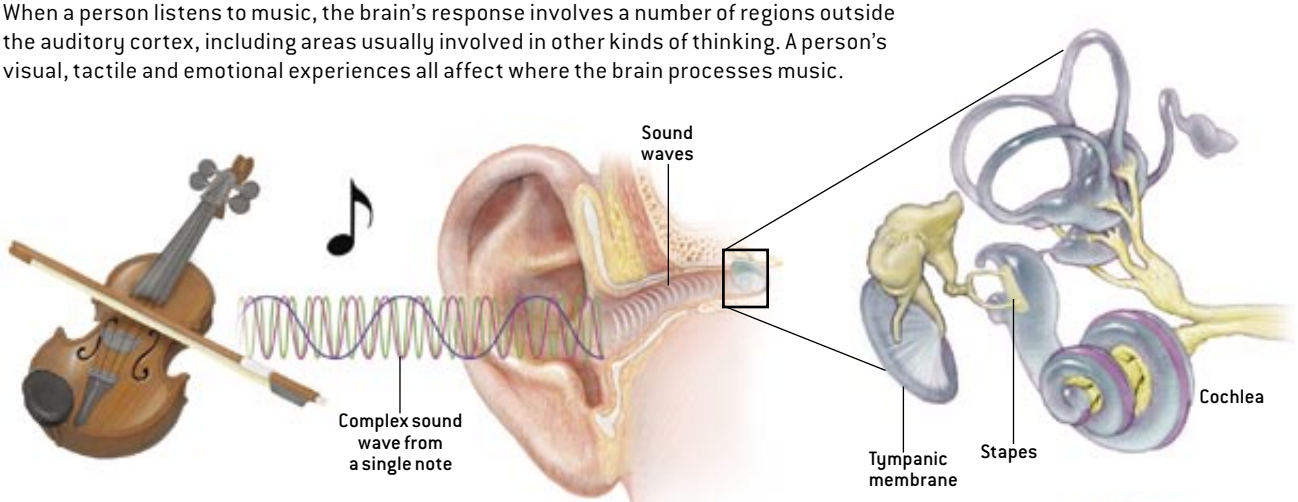
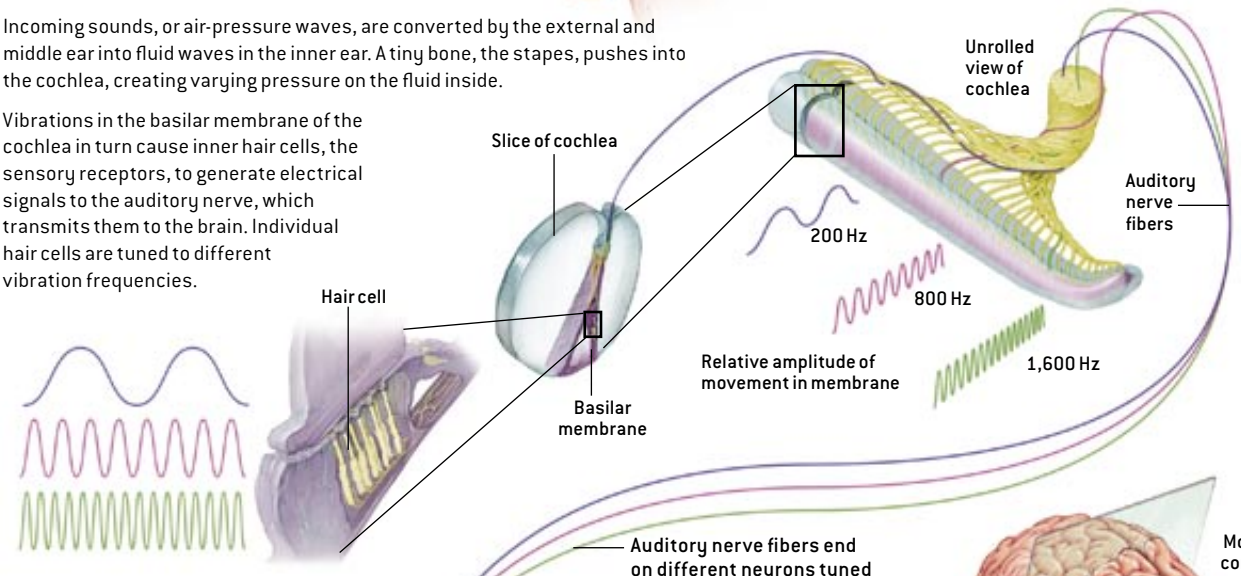
Singing in the Brain

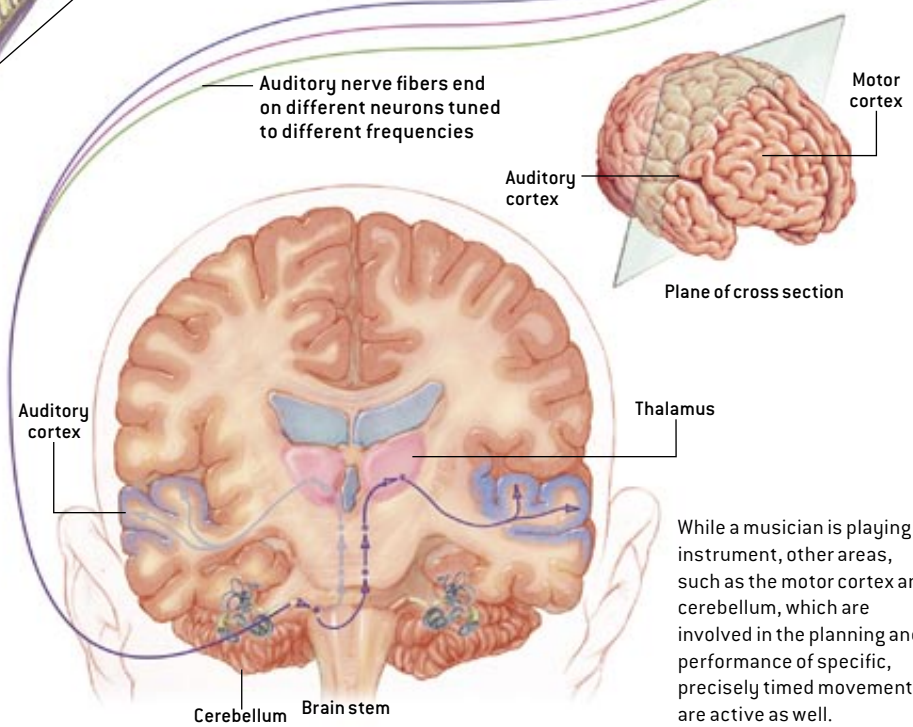
When a person listens to music, the brain's response involves a number of regions outside the auditory cortex, including areas usually involved in other kinds of thinking. A person's visual, tactile and emotional experiences all affect where the brain processes music.



Incoming sounds, or air-pressure waves, are converted by the external and middle ear into fluid waves in the inner ear. A tiny bone, the stapes, pushes into the cochlea, creating varying pressure on the fluid inside.

Vibrations in the basilar membrane of the cochlea in turn cause inner hair cells, the sensory receptors, to generate electrical signals to the auditory nerve, which transmits them to the brain. Individual hair cells are tuned to different vibration frequencies.





The brain processes music both hierarchically and in a distributed manner. Within the overall auditory cortex, the primary auditory cortex, which receives inputs from the ear and lower auditory system via the thalamus, is involved in early stages of music perception, such as pitch (a tone's frequency) and contour (the pattern of changes in pitch), which is the basis for melody. The primary auditory cortex is "retuned" by experience so that more cells become maximally responsive to important sounds and musical tones. This learning-induced retuning affects further cortical processing in areas such as secondary auditory cortical fields and related so-called auditory association regions, which are thought to process more complex music patterns of harmony, melody and rhythm.

While a musician is playing an instrument, other areas, such as the motor cortex and cerebellum, which are involved in the planning and performance of specific, precisely timed movements, are active as well.

ANDREW SWIFT

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areas of the brain are involved in processing the various components of music. Consider tone, which encompasses both the frequencies and loudness of a sound. At one time, investigators suspected that cells tuned to a specific frequency always responded the same way when that frequency was detected.

But in the late 1980s David Diamond, Thomas M. McKenna and I, working in my laboratory at the University of California, Irvine, raised doubts about that notion when we studied contour, which is the pattern of rising and falling pitches that is the basis for all melodies. We constructed melodies consisting of different contours using the same five tones and then recorded the responses of single neurons in the auditory cortices of cats. We found that cell responses (the number of discharges) varied with the contour. Responses depended on the location of a given tone within a melody; cells may fire more vigorously when that tone is preceded by other tones rather than when it is the first. Moreover, cells react differently to the same tone when it is part of an ascending contour (low to high tones) than when it is part of a descending or more complex one. These findings show that the pattern of a melody matters: processing in the auditory system is not like the simple relaying of sound in a telephone or stereo system.

Most research has focused on melody, but rhythm (the relative lengths and spacing of notes), harmony (the relation of two or more simultaneous tones) and timbre (the characteristic difference in sound between two instruments playing the same tone) are also of interest. Studies of rhythm have concluded that one hemisphere is more involved, although they disagree on which hemisphere. The problem is that different tasks and even different rhythmic stimuli can demand different processing capacities. For example, the left temporal lobe seems to process briefer stimuli than the right temporal lobe and so would be more involved when the listener is trying to discern rhythm while hearing briefer musical sounds.

The situation is clearer for harmony. Imaging studies of the cerebral cortex find greater activation in the auditory regions of the right temporal lobe when subjects are focusing on aspects of harmony. Timbre also has been "assigned" a right temporal lobe preference. Patients whose temporal lobe has been removed (such as to eliminate seizures) show deficits in discriminating timbre if tissue from the right, but not the left, hemisphere is excised. In addition, the right temporal lobe becomes active in normal subjects when they discriminate between different timbres.

Brain responses also depend on the experiences and training of the listener. Even a little training can quickly alter the brain's reactions. For instance, until about 10 years ago, scientists believed that tuning was "fixed" for each cell in the auditory cortex. Our studies on contour, however, made us suspect that cell tuning might be altered during learning so that certain cells become extra sensitive to sounds that attract attention and are stored in memory.

Learning retunes the brain so that more cells respond best to behaviorally significant sounds.

To find out, Jon S. Bakin, Jean-Marc Edeline and I conducted a series of experiments during the 1990s in which we asked whether the basic organization of the auditory cortex changes when a subject learns that a certain tone is somehow important. Our group first presented guinea pigs with many different tones and recorded the responses of various cells in the auditory cortex to determine which tones produced the greatest responses. Next, we taught the subjects that a specific, nonpreferred tone was important by making it a signal for a mild foot shock. The guinea pigs learned this association within a few minutes. We then determined the cells' responses again, immediately after the training and at various times up to two months later. The neurons' tuning preferences had shifted from their original frequencies to that of the signal tone. Thus, learning retunes the brain so that more cells respond best to behaviorally significant sounds. This cellular adjustment process extends across the cortex, "editing" the frequency map so that a greater area of the cortex processes important tones. One can tell which frequencies are important to an animal simply by determining the frequency organization of its auditory cortex [*see box on opposite page*].

The retuning was remarkably durable: it became stronger over time without additional training and lasted for months. These findings initiated a growing body of research indicating that one way the brain stores the learned importance of a stimulus is by devoting more brain cells to the processing of that stimulus. Although it is not possible to record from single neurons in humans during learning, brain-imaging studies can detect changes in the average magnitude of responses of thousands of cells in various parts of the cortex. In 1998 Ray Dolan and his colleagues at University College London trained human subjects in a similar type of task by teaching

THE AUTHOR

NORMAN M. WEINBERGER, who received his Ph.D. in experimental psychology from Western Reserve University, works in the department of neurobiology and behavior at the University of California, Irvine. He is a founder of U.C.I.'s Center for the Neurobiology of Learning and Memory and of MuSICA (Music and Science Information Computer Archive). A pioneer in the field of learning and memory in the auditory system, Weinberger is on the editorial board of the journal *Neurobiology of Learning and Memory.*

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them that a particular tone was significant. The group found that learning produces the same type of tuning shifts seen in animals. The long-term effects of learning by retuning may help explain why we can quickly recognize a familiar melody in a noisy room and also why people suffering memory loss from neurodegenerative diseases such as Alzheimer's can still recall music that they learned in the past.

Even when incoming sound is absent, we all can "listen" by recalling a piece of music. Think of any piece you know and "play" it in your head. Where in the brain is this music playing? In 1999 Andrea R. Halpern of Bucknell University and Robert J. Zatorre of the Montreal Neurological Institute at McGill University conducted a study in which they scanned the brains of nonmusicians who either listened to music or imagined hearing the same piece of music. Many of the same areas in the temporal lobes that were involved in listening to the melodies were also activated when those melodies were merely imagined.

Well-Developed Brains

STUDIES OF MUSICIANS have extended many of the findings noted above, dramatically confirming the brain's ability to revise its wiring in support of musical activities. Just as some training increases the number of cells that respond to a sound when it becomes important, prolonged learning produces more marked responses and physical changes in the brain. Musicians, who usually practice many hours a day for years, show such effects—their responses to music differ from those of nonmusicians; they also exhibit hyperdevelopment of certain areas in their brains.

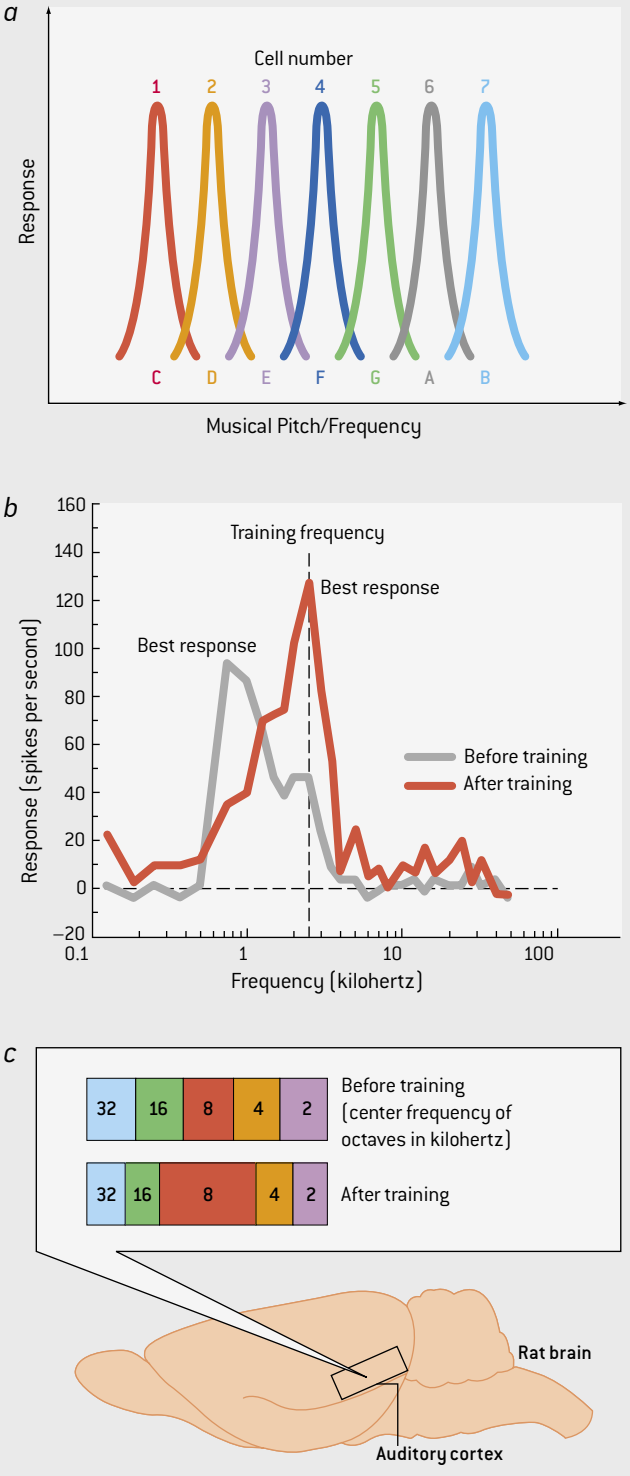
Christo Pantev, then at the University of Münster in Germany, led one such study in 1998. He found that when musicians listen to a piano playing, about 25 percent more of their left hemisphere auditory regions respond than do so in nonmusicians. This effect is specific to musical tones and does not occur with similar but nonmusical sounds. Moreover, the authors found that this expansion of response area is greater the younger the age at which lessons began. Studies of children suggest that early musical experience may facilitate development. In 2004 Antoine Shahin, Larry E. Roberts and Laurel J. Trainor of McMaster University in Ontario recorded brain responses to piano, violin and pure tones in four- and five-year-old children. Youngsters who had received greater exposure to music in their homes showed enhanced brain auditory activity, comparable to that of unexposed kids about three years older.

Musicians may display greater responses to sounds, in part because their auditory cortex is more extensive. Peter Schneider and his co-workers at the University of Heidelberg in Germany reported in 2002 that the volume of this cortex in musicians was 130 percent larger. The percentages of volume increase were linked to levels of musical training, suggesting that learning music proportionally increases the number of neurons that process it.

In addition, musicians' brains devote more area toward

Retuning the Brain

Individual brain cells each respond optimally to a particular pitch or frequency (*a*). Cells shift their original tuning when an animal learns that a specific tone is important (*b*). This cellular adjustment "edits" the "frequency map" of a rat's brain so that a greater area of the cortex processes an important tone—for instance, it expands the map for eight kilohertz when that is the important frequency (*c*).



LAURIE GRACE

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motor control of the fingers used to play an instrument. In 1995 Thomas Elbert of the University of Konstanz in Germany and his colleagues reported that the brain regions that receive sensory inputs from the second to fifth (index to pinkie) fingers of the left hand were significantly larger in violinists; these are precisely the fingers used to make rapid and complex movements in violin playing. In contrast, they observed no enlargement of the areas of the cortex that handle inputs from the right hand, which controls the bow and requires no special finger movements. Nonmusicians do not exhibit these differences. Further, Pantev, now at the Rotman Research Institute at the University of Toronto, reported in 2001 that the brains of professional trumpet players react in such an intensified manner only to the sound of a trumpet—not, for example, to that of a violin.

Musicians must also develop greater ability to use both hands, particularly for keyboard playing. Thus, one might expect that this increased coordination between the motor regions of the two hemispheres has an anatomical substrate. That seems to be the case. The anterior corpus callosum, which contains the band of fibers that interconnects the two motor areas, is larger in musicians than in nonmusicians. Again, the extent of increase is greater the earlier the music lessons began. Other studies suggest that the actual size of the motor cortex, as well as that of the cerebellum—a region at the back of the brain involved in motor coordination—is greater in musicians.

Ode to Joy—or Sorrow

BEYOND EXAMINING HOW the brain processes the auditory aspects of music, investigators are exploring how it evokes strong emotional reactions. Pioneering work in 1991 by John A. Sloboda of Keele University in England revealed that more than 80 percent of sampled adults reported physical responses to music, including thrills, laughter or tears. In a 1995 study by Jaak Panksepp of Bowling Green State University, 70 percent of several hundred young men and woman polled said that they enjoyed music "because it elicits emotions and feelings." Underscoring those surveys was the result of a 1997 study by Carol L. Krumhansl of Cornell Univer-

Born to Rock?

Although many people think they are musically impaired, we are all musical to some degree. In fact, to find someone with a "musical brain," we need only look at any infant. Even before babies have acquired language, they exhibit a marked capacity for reacting to music. Perhaps that is why parents and others instinctively communicate with infants in a musical manner, using wide ranges of pitch and melodiclike phrases, often called "motherese." All cultures use motherese.

Beyond reacting positively to such communication, infants appear to encourage the performance of their mothers. In a 1999 study by Laura-Lee Balkwill and William F. Thompson, both then at York University in Toronto, North American and East Indian mothers sang the same song both with their infant present and absent. Others later were able to judge accurately in which of the two recordings the infant was present. The study showed as well that at least some musical cues appear to play across cultures. Listeners to the recordings could tell if the infant had been present or not regardless of whether they heard the song in their own language or in another.

How do we know infants are aware of music when they can't yet talk? We use objective measures of their behavior. For example, an infant sits on his mother's lap. To the left and right are two loudspeakers and adjacent transparent plastic boxes. Each box is ordinarily dark, but when the tot turns his head toward one it rewards him by lighting up and activating an animated toy, such as a dog or monkey. During testing, a researcher manipulates puppets or other objects directly in front of the baby to attract attention. A musical stimulus (which can be a single tone or a melody) plays repeatedly from one loudspeaker. At random times, the experimenter pushes a hidden button that changes the stimulus. If the infant notices the difference and turns toward the speaker, he is rewarded with the sight of the toy.

Musical communication, the singsong way of speaking to infants known as "motherese," is common in all cultures.

Such tests have revealed that infants differentiate between two adjacent musical tones as well as adults. Babies also notice changes in both tempo, the speed at which music is played, and rhythm. And they recognize a melody when it is played in a different key. Underscoring such studies, Laurel J. Trainor of McMaster University in Ontario found that babies as young as two to six months prefer consonant sounds to dissonant ones. Music learning appears to begin even earlier, however—in utero. Peter Hepper of Queen's University in Belfast found that about two weeks before birth, fetuses recognized the difference between the theme music of the *Neighbors* TV show, heard daily by their mothers for weeks, and a novel song. —*N.M.W.*

IT INTERNATIONAL/ESTOCK PHOTO

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Bone flute from a site in France dates back at least 32,000 years—evidence that humans have been playing music since the dawn of culture.

sity. She and her co-workers recorded heart rate, blood pressure, respiration and other physiological measures during the presentation of various pieces that were considered to express happiness, sadness, fear or tension. Each type of music elicited a different but consistent pattern of physiological change across subjects.

Until recently, scientists knew little about the brain mechanisms involved. One clue, though, comes from a woman known as I.R. (initials are used to maintain privacy) who suffered bilateral damage to her temporal lobes, including auditory cortical regions. Her intelligence and general memory are normal, and she has no language difficulties. Yet she can make no sense of nor recognize any music, whether it is a previously known piece or a new piece that she has heard repeatedly. She cannot distinguish between two melodies no matter how different they are. Nevertheless, she has normal emotional reactions to different types of music; her ability to identify an emotion with a particular musical selection is completely normal! From this case we learn that the temporal lobe is needed to comprehend melody but not to produce an emotional reaction, which is both subcortical and involves aspects of the frontal lobes.

An imaging experiment in 2001 by Anne Blood and Zatorre of McGill sought to better specify the brain regions involved in emotional reactions to music. This study used mild emotional stimuli, those associated with people's reactions to musical consonance versus dissonance. Consonant musical intervals are generally those for which a simple ratio of frequencies exists between two tones. An example is middle C (about 260 hertz, or Hz) and middle G (about 390 Hz). Their ratio is 2:3, forming a pleasant-sounding "perfect fifth" interval when they are played simultaneously. In contrast, middle C and C sharp (about 277 Hz) have a "complex" ratio of about 17:18 and are considered unpleasant, having a "rough" sound.

What are the underlying brain mechanisms of that experience? PET (positron-emission tomography) imaging conducted while subjects listened to consonant or dissonant chords showed that different localized brain regions were involved in the emotional reactions. Consonant chords activated the orbitofrontal area (part of the reward system) of the right hemisphere and also part of an area below the corpus callosum. In contrast, dissonant chords activated the right parahippocampal gyrus. Thus, at least two systems, each dealing with a different type of emotion, are at work when the brain processes emotions related to music. How the different patterns of activity in the auditory system might be specifically linked to these differentially reactive regions of the hemispheres remains to be discovered.

In the same year, Blood and Zatorre added a further clue to how music evokes pleasure. When they scanned the brains of musicians who experienced chills of euphoria when listening to music, they found that music activated some of the same reward systems that are stimulated by food, sex and addictive drugs.

Music activates the same reward systems that are stimulated by **food, sex and addictive drugs.**

Overall, findings to date indicate that music has a biological basis and that the brain has a functional organization for music. It seems fairly clear, even at this early stage of inquiry, that many brain regions participate in specific aspects of music processing, whether supporting perception (such as apprehending a melody) or evoking emotional reactions. Musicians appear to have additional specializations, particularly hyperdevelopment of some brain structures. These effects demonstrate that learning retunes the brain, increasing both the responses of individual cells and the number of cells that react strongly to sounds that become important to an individual. As research on music and the brain continues, we can anticipate a greater understanding not only about music and its reasons for existence but also about how multifaceted it really is. SA

MORE TO EXPLORE

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Blind and sighted people use many of the same devices in sketching their surroundings, suggesting that vision and touch are closely linked

BY JOHN M. KENNEDY

How the BLIND DRAW

Outline drawings, made by Kathy, totally blind since age three, demonstrate that blind artists use many of the same devices as sighted illustrators do. They use lines to represent surfaces, as Kathy's picture of the eagle on her charm bracelet shows (*top left*). Blind people portray objects, such as a house, from a single vantage point (*bottom left*). Blind artists use shapes to convey abstract messages: Kathy drew a heart surrounding a crib to describe the love surrounding a child (*bottom right*). And they use foreshortening to suggest perspective: Kathy drew the L-shaped block and the cube to be the same size when they were side by side but made the cube smaller when it was placed farther away from her (*top right*).

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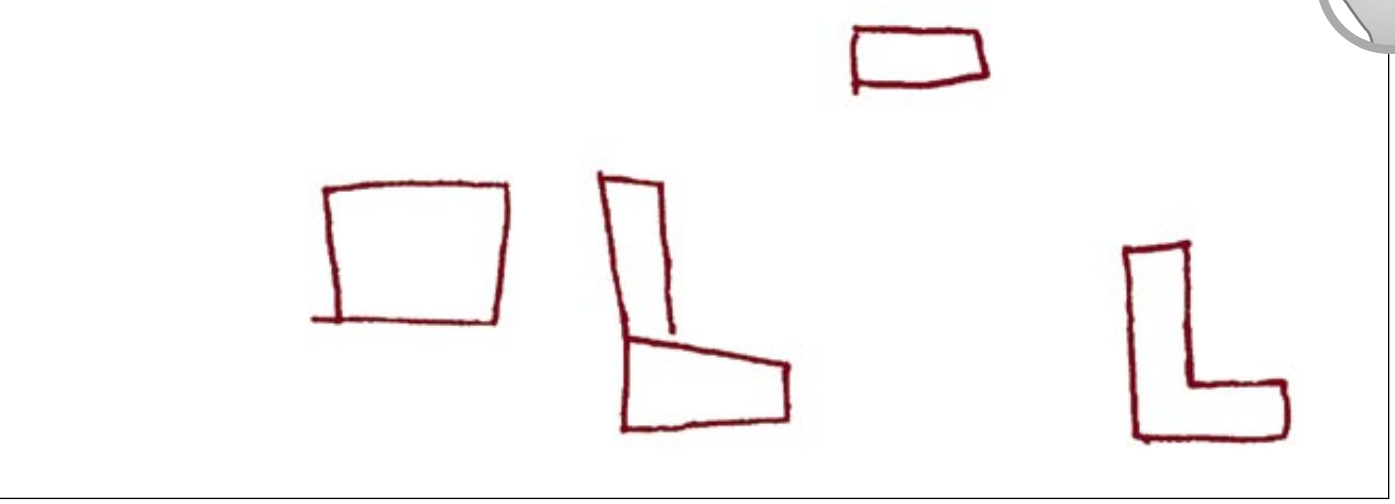

DRAWINGS COURTESY OF JOHN M. KENNEDY

I first met Betty, a blind teenager in Toronto, as I was interviewing participants for an upcoming study of mine on touch perception in 1973. Betty had lost her sight at age two, when she was too young to have learned how to draw. So I was astonished when she told me that she liked to draw profiles of her family members. Before I began working with the blind, I had always thought of pictures as copies of the visible world. After all, we do not draw sounds, tastes or smells; we draw what we see. Thus, I had assumed that blind people would have little interest or talent in creating images. But as Betty's comments revealed that day, I was very wrong. Relying on her imagination and sense of touch, Betty enjoyed tracing out the distinctive shape of an individual's face on paper.

I was so intrigued by Betty's ability that I wanted to find out if other blind people could readily make useful illustrations—and if these drawings would be anything like the pictures sighted individuals use. In addition, I hoped to discover whether the blind could interpret the symbols commonly used by sighted people. To bring the blind into the flat, graphical world of the sighted, I turned to a number of tools, including models, wire displays and, most often, raised-line drawing kits, made available by the Swedish Organization for the Blind. These kits are basically stiff boards covered with a layer of rubber and a thin plastic sheet. The pressure from any ballpoint pen produces a raised line on the plastic sheet.

Thanks to this equipment, my colleagues and I have made some remarkable findings over the past 30 years, and this information has revised our understanding of sensory perception. Most significantly, we have learned that blind and sighted people share a form of pictorial shorthand. That is, they adopt many of the same devices in sketching their surroundings: for example, both groups use lines to represent the edges of surfaces. Both employ foreshortened shapes and converging lines to convey depth. Both typically portray scenes from a single vantage point. Both render extended or irregular lines to connote motion. And both use shapes that are symbolic, though not always visually correct, such as a heart or a star, to relay

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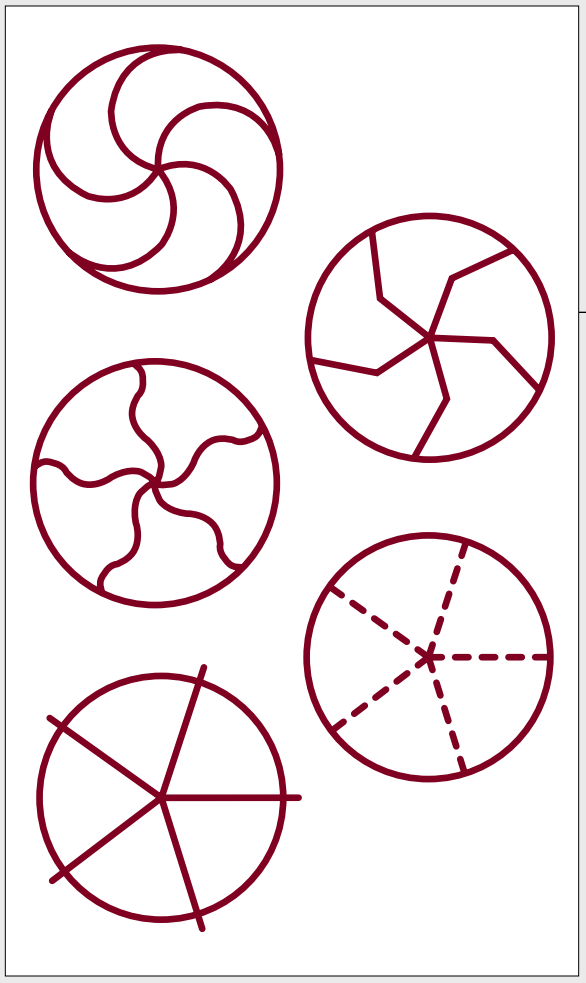
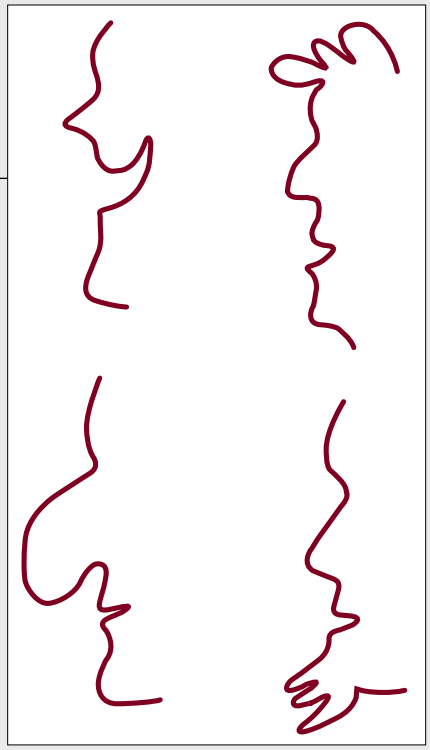
Shape Recognition



Motion can be suggested by irregular lines. When blind and sighted volunteers were shown five diagrams of moving wheels (*left*), they generally interpreted them in the same way. Most guessed that the curved spokes indicated that the wheel was spinning steadily; the wavy spokes, they thought, suggested that the wheel was wobbling; and the bent spokes were taken as a sign that the wheel was jerking. Subjects assumed that spokes extending beyond the wheel's perimeter signified that the wheel had its brakes on and that dashed spokes indicated that the wheel was spinning quickly.



Profiles, made from plastic-coated wires mounted on a thin metal board, were given to nine blind subjects in Stockholm. The subjects were asked to describe each display using one of four labels: smile, curly hair, beard or large nose. On average, the group described 2.8 of the four displays accurately, showing that blind people often recognize the outline of simple objects. Blindfolded, sighted control subjects given the same task did only slightly better.

abstract messages. In sum, our work shows that even very basic pictures reflect far more than meets the eye.

Outlines

AFTER MEETING BETTY, I began to wonder whether all blind people could appreciate facial profiles shown in outline. Over the years, I asked blind volunteers in North America and Europe to draw profiles of several kinds of objects. In the 1990s I undertook a series of studies with Yvonne Eriksson of Linköping University and the Swedish Library of Talking Books and Braille. In 1993 we tested nine adults from Stockholm—three men and six women. Four were congenitally blind, three had lost their sight after the age of three, and two had minimal vision. Each subject examined four raised profiles, which Hans-Joergen Andersen, an undergraduate psychology student at Aarhus University in Denmark, made by gluing thin, plastic-coated wires to a flat metal board [*see right panel above*].

Eriksson and I asked the volunteers to describe the most prominent feature on each display using one of four labels: smile, curly hair, beard or large nose. Five of them—including one man who had been totally blind since birth—correctly identified all four pictures. Only one participant recognized none. On average, the group labeled 2.8 of the four outlines accurately. In comparison, when 18 sighted undergraduates in Toronto were blindfolded and given the same raised-line profiles, they scored only slightly better, matching up a mean of 3.1 out of four displays.

Many investigators in the U.S., Japan, Norway, Sweden, Spain and the U.K. have reported similar results, leav-

THE AUTHOR

JOHN M. KENNEDY was born in Belfast in 1942 and was raised in one of the few Unitarian families in Northern Ireland. He attended the Royal Belfast Academical Institution and Queen's University of Belfast, where his interests included fencing and theater. He completed his Ph.D. in perception at Cornell University and began his research with the blind shortly thereafter as an assistant professor at Harvard University. He is currently professor of psychology at the University of Toronto at Scarborough and a Fellow of the Royal Society of Canada. His home page is located at www.utsc.utoronto.ca/~kennedy

COURTESY OF JOHN M. KENNEDY

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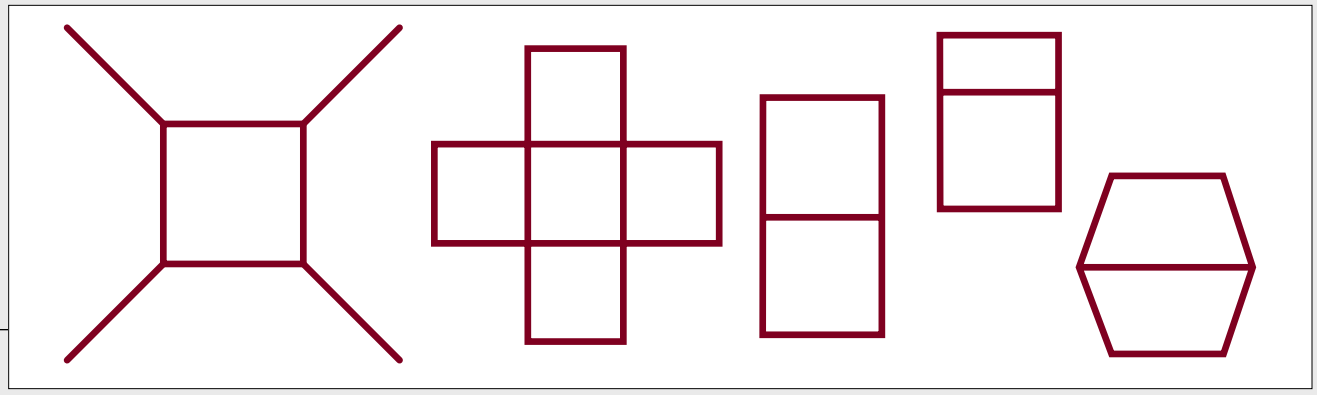
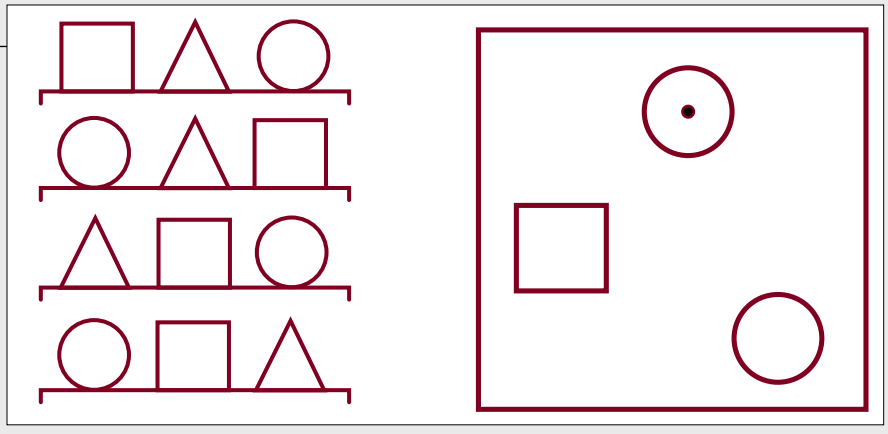


Perspective is readily understood by the blind. To prove this point, the author and Paul Gabias of the University of British Columbia at Okanagan asked 24 congenitally blind volunteers to examine a drawing of a table (*far left*) and four drawings of a cube. They were told that one blind person drew the table in a star shape to show how it appeared from underneath and that another blind person drew an identical table, intending to show its symmetry instead. The subjects were then asked which cube was most likely drawn by the person who drew the table from underneath. Most chose the cube composed of two trapeziums (*far right*), the one that made the most sophisticated use of perspective.



Solids—a sphere, a cone and a cube—arranged on a table are commonly used to test spatial ability. The arrangement is shown from overhead at the far right. Which drawing at the near right shows the solids from the edge of the table facing the bottom of the page? Which drawing shows them from the opposite edge? From the edge facing left? Facing right? Blind and sighted individuals do equally well on this task, proving that the blind can determine how objects appear from particular vantage points.

ing little doubt that blind people can recognize the outline shape of familiar objects. At first, it may seem odd that even those who have never had any vision whatsoever possess some intuitive sense of how faces and other objects appear. But with further thought, the finding makes perfect sense. The lines in most simple drawings show one of two things: where two surfaces overlap, called an occluding edge, or where two surfaces meet in a corner. Neither feature need be seen to be perceived. Both can be discerned by touching.

Not all blind people read raised-line drawings equally well, and these individual discrepancies can reflect the age at which someone lost his or her sight. For example, people who have been blind from birth or infancy—termed the early blind—sometimes find raised-line drawings challenging. But in 1993 Yatuka Shimizu of Tsukuba University of Technology in Japan, with colleagues Shinya Saida and Hiroshi Shimura, studied early-blind subjects and found that they recognized 60 percent of a set of outline pictures of common objects, such as a fish or a bottle. Recognition rates were somewhat higher for sighted, blindfolded subjects, who are more familiar with pictures in general.

Interestingly, subjects who lose vision later in life—called the later blind—frequently interpret raised outlines more readily than either sighted or early-blind individuals do, according to Morton Heller of Eastern Illinois University. One likely explanation is that the later blind have a double advantage in these tasks: they are typically more familiar with pictures than are the early blind, and they have much better tactile skills than do the sighted.

Perspective

JUST AS BETTY prompted me to study whether the blind appreciate profiles in outline, another amateur artist, Kathy from Ottawa, led me to investigate a different question. Kathy first participated in my studies when she was 30 years old. Because of retinal cancer detected during her first year of life, Kathy had been totally blind since age three and had never had detailed vision. Even so, she was quite good at making raised-line drawings. On one occasion Kathy sketched several different arrangements of a cube and an L-shaped block that I

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Blind artists, such as Tracy (*above*), rely on their sense of touch to render familiar objects. Tracy lost all sight to retinal cancer at the age of two, but by feeling the glass, she determines its shape. By rubbing the paper, placed on a piece of felt, she knows where her pen has scored the page and left a mark. Because the lines in most simple drawings reveal surface edges—features that are discerned by touching as readily as they are by sight—drawings by the blind are easily recognized by sighted people.

ABRAHAM MENASHE (www.humanistic-photography.com)

used to test how relative distances appear in line art. When the blocks sat side by side, she made them the same size—as they were in actuality. But when the cube was farther from her than the other block, she made it smaller in her drawing.

This second drawing revealed a fundamental principle of perspective—namely, that as an object becomes more distant, it subtends a smaller angle. (Think about viewing a picket fence at an angle and how its posts appear shorter closer to the horizon.) Kathy's use of this basic rule suggested that some aspects of perspective might be readily understood by the blind. Again the proposition seemed reasonable, given some consideration. Just as we see objects from a particular vantage point, so, too, do we reach out for them from a certain spot. For proof of the theory, I designed a study with Paul Gabias of the University of British Columbia at Okanagan, who was then at New York University.

We prepared five raised-line drawings: one of a table and four of a cube [*see top illustration on preceding page*]. We showed the drawings to 24 congenitally blind volunteers and asked them a series of questions. The table drawing had a central square and four legs, one protruding from each corner. The subjects were told that a blind person had drawn the table and had explained, "I've drawn it this way to show that it is symmetrical on all four sides." They were then told that another blind person had drawn an identical table but had offered a different explanation: "I've shown it from underneath in order to show the shape of the top and all four legs. If you show the table from above or from the side, you can't really show the top and all four legs, too."

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Next we asked our volunteers to pick out the cube drawing that had most likely been made by the person who drew the table from below. To answer consistently, they needed to understand what strategy had been used in drawing the table and each cube. One cube resembled a foldout of a box, showing the front face of the cube in the middle, surrounded by its top, bottom, left and right faces. Another drawing showed two squares, representing the front and top of the cube. A third picture depicted the front of the cube as a square and the top as a rectangle—foreshortened because it was receding away from the observer. A fourth illustrated two trapeziums joined along the longest line; the extra length of this line revealed that it was the edge nearest to the observer.

Words Associated with Circle-Square	Agreement among Subjects (percent)
Soft-Hard	100
Mother-Father	94
Happy-Sad	94
Good-Evil	89
Love-Hate	89
Alive-Dead	87
Bright-Dark	87
Light-Heavy	85
Warm-Cold	81
Summer-Winter	81
Weak-Strong	79
Fast-Slow	79
Cat-Dog	74
Spring-Fall	74
Quiet-Loud	62
Walking-Standing	62
Odd-Even	57
Far-Near	53
Plant-Animal	53
Deep-Shallow	51

Which cube do you think was drawn by the person who intended to show the table from below? Most of the blind volunteers chose the drawing that showed two trapeziums. That is, they selected the illustration that made the most sophisticated use of perspective. Accordingly, they picked as the least likely match the flat "foldout" drawing—the one that used no perspective whatsoever. The foldout drawing was also the one they judged most likely to have been made by the person who, in drawing the table, had hoped to highlight its symmetry.

Heller and I joined forces to prepare another task for demonstrating that the blind understood the use of perspective. (You might like to try it, too; see the bottom illustration on page 47.) We arranged three solids—a sphere, a cone and a cube—on a rectangular tabletop. Our blind subjects sat on one side. We asked them to draw the objects from where they were sitting and then to imagine four different views: from the other three sides of the table and from directly above as well. (Swiss child psychologist Jean Piaget called this exercise the perspective-taking, or "three mountains," task.) Many adults and children find this problem quite difficult. On average, however, our blind subjects performed as well as sighted control subjects, drawing 3.4 of the five images correctly.

Next, we asked our subjects to name the vantage point used in five separate drawings of the three objects. We presented the drawings to them twice, in random order, so that the highest possible score was 10 correct. Of that total, the blind subjects named an average of 6.7 correctly. Sighted subjects scored only a little higher, giving 7.5 correct answers on average. The nine later-blind subjects in the study fared slightly better than the congenitally blind and the sighted, scoring 4.2 on the drawing task and 8.3 on the recognition task. Again, the later blind probably scored so well because they have a familiarity with pictures and enhanced tactile skills.

Word pairs were used to test the symbolism in abstract shapes—and whether blind and sighted people perceived such meanings in the same way. Subjects were told that in each pair of words, one fit best with circle and the other with square. For example, which shape better describes soft? According to the number given after the soft-hard word pair, everyone thought a circle did. These percentages show the level of consensus among sighted subjects. Blind volunteers made similar choices.

It is clear that blind people can appreciate the use of outlines and perspective to describe the arrangement of objects.

Metaphor

FROM THE STUDIES described above, it is clear that blind people can appreciate the use of outlines and perspective to describe the arrangement of objects and other surfaces in space. But pictures are more than literal representations. This fact was drawn to my attention dramatically when a blind woman in one of my investigations decided on her own initiative to draw a wheel as it was spinning. To show this motion, she traced a curve inside the circle. I was taken aback. Lines of motion, such as the one she used, are a very recent invention in the history of illustration. Indeed, as art scholar David Kunzle notes, Wilhelm Busch, a trendsetting 19th-century cartoonist, used virtually no motion lines in his popular figures until about 1877.

When I asked several other blind study subjects to draw a spinning wheel, one particularly clever rendition appeared repeatedly: several subjects drew the wheel's spokes as curved lines. When asked about these curves, they all described them as metaphorical ways of suggesting motion. Majority rule would argue that this device somehow indicated motion very well. But was it a better indicator than, say, broken or wavy lines—or any other kind of line, for that matter? The answer was not clear. So I decided to test whether various lines of

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motion were apt ways of showing movement or if they were merely idiosyncratic marks. Moreover, I wanted to discover whether there were differences in how the blind and the sighted interpreted lines of motion.

To search out these answers, Gabias and I created raised-line drawings of five different wheels, depicting spokes with lines that curved, bent, waved, dashed and extended beyond the perimeter of the wheel. We then asked 18 blind volunteers to assign one of the following motions to each wheel: wobbling, spinning fast, spinning steadily, jerking or braking. Which wheel do you think fits with each motion? Our control group consisted of 18 sighted undergraduates from the University of Toronto.

All but one of the blind subjects assigned distinctive motions to each wheel. In addition, the favored description for the sighted was the favored description for the blind in every instance. What is more, the consensus among the sighted was barely higher than that among the blind. Because motion devices are unfamiliar to the blind, the task we gave them involved some problem solving. Evidently, however, the blind not only figured out meanings for each line of motion, but as a group they generally came up with the same meaning—at least as frequently as did sighted subjects.

We have found that the blind understand other kinds of visual metaphors as well. Kathy once drew a child's crib inside a heart—choosing that symbol, she said, to show that love surrounded the child. With Chang Hong Liu, now at the University of Hull in England, I began exploring how well blind people understand the symbolism behind shapes such as hearts, which do not directly represent their meaning. We gave a list of 20 pairs of words to sighted subjects and asked them to pick from each pair the term that best related to a circle and the term that best related to a square. (If you wish to try this yourself, the list of words can be found on the preceding page.) For example, we asked: What goes with soft? A circle or a square? Which shape goes with hard?

All our subjects deemed the circle soft and the square hard. A full 94 percent ascribed happy to the circle, instead of sad. But other pairs revealed less agreement: 79 percent matched fast and slow to circle and square, respectively. And only 51 percent linked deep to circle and shallow to square. When we tested four totally blind volunteers using the same list, we found that their choices closely resembled those made by the sighted subjects. One man, who had been blind since birth, scored extremely well. He made only one match differing from the consensus, assigning "far" to square and "near" to circle. In fact, only a small majority of sighted subjects—53 percent—had paired far and near to the opposite partners. Thus, we concluded that the blind interpret abstract shapes as sighted people do.

Perception

WE TYPICALLY THINK of sight as the perceptual system by which shapes and surfaces speak to the mind. But as the empirical evidence discussed above demonstrates, touch can relay much of the same information. In some ways, this finding is not so surprising. When we see something, we know more or less how it will feel to the touch, and vice versa. Even so, touch and sight are two very different senses: one receives input in the form of pressure, and one responds to changes in light. How is it that they can then interpret something as simple as a line in exactly the same way? To answer this question, we must consider what kind of information it is that outlines impart to our senses.

The most obvious theory is that each border in a basic drawing represents one physical boundary around some surface or shape. But it is not that simple, because all lines, no matter how thin, have two sides or contours—an inside and an outside border, if you will. As a result, thick lines are perceived quite differently from thin ones. Consider a thick line tracing a profile. If it is thick enough, it appears to show two profiles, one per edge, gazing in the same direction [*see illustration below*]. When the line is thin and its two borders

When we see something, we know more or less how it will feel to the touch, and vice versa.

COURTESY OF JOHN M. KENNEDY

Thickness of these outlines determines whether their two contours are viewed as one profile or two. The same ambiguity occurs with touch. Blind subjects interpret raised edges placed near each other as a single surface boundary and those placed farther apart as two.

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are close together, though, an observer perceives only one face. As it turns out, touch produces a similar effect. I prepared a series of profile drawings in which both edges of the defining line were raised. When the edges were only 0.1 centimeter apart, my blind volunteer, Sanne, a student at Aarhus University, said they showed one face. When they were 0.8 centimeter apart, she reported that they showed two faces.

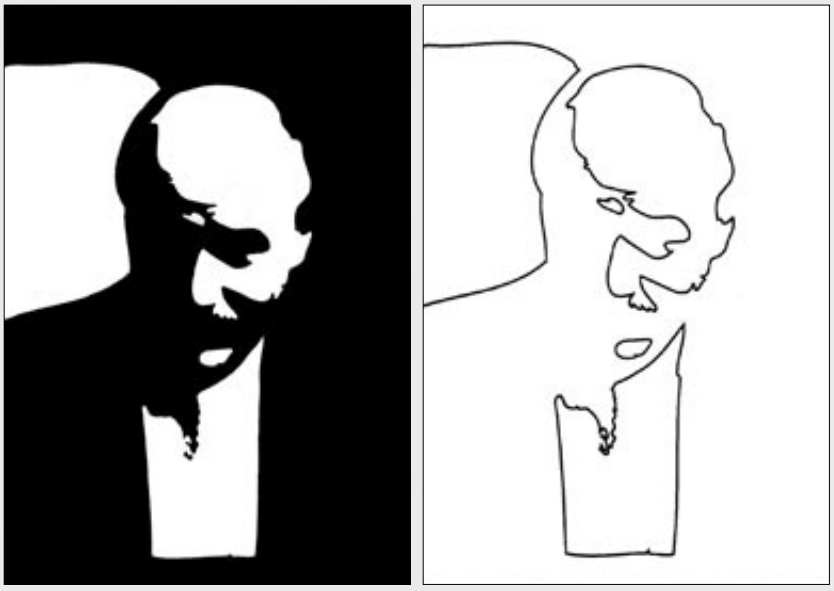
Another theory of outline drawings suggests that lines substitute for any perceptible boundary, including those that are not tangible, such as shadows. But this theory, too, fails in a very telling fashion. Look at the illustration at the right, which shows two pictures of the author. In one image, shadow patterns, defined by a single contour separating light and dark areas, cross my face. In the second image, a dark line having two contours traces the same shadow patterns. Despite the fact that the shapes in the second picture are identical to those in the first, the perceptual results are vividly different. The first is easily recognized as a face; the second is not.

Again, this example shows that our visual system, like our tactile system, does not read two contours of a line in the same way as it interprets a single contour. The implication is that the brain region responsible for interpreting contours in sensory input from busy environments is a general surface-perception system. As such, it does not discriminate on the basis of purely visual matters, such as brightness and color. Rather it takes the two contours of a dark line and treats them as indicators for the location of a single edge of some surface. Whereas sighted individuals treat brightness borders as indicators of surface edges, the blind treat pressure borders in the same way.

Because the principles at work here are not just visual, the brain region that performs them could be called multimodal or, as it is more commonly termed, amodal. In one account, which I have discussed in my book on drawings by the blind, such an amodal system receives input from both vision and touch. The system considers the input as information about such features as occlusion, foreground and background, flat and curved surfaces, and vantage points. In the case of the sighted, visual and tactile signals are coordinated by this amodal system.

As we have found, the ability to interpret surface edges functions even when it does not receive any visual signals. It is for this very reason that the blind so readily appreciate line drawings and other graphic symbols. Knowing this fact should encourage scholars and educators to prepare materials for the blind that make vital use of pictures. Several groups around the world are doing just that. For instance, Art Education for the Blind, an organization associated with the Whitney Museum of American Art and the Museum of Modern Art in New York City, has prepared raised-line versions of Henri Matisse paintings and of cave art. It may not be long before raised pictures for the blind are as well known as Braille texts. SA

Borders of Understanding



Shadows, and other intangible boundaries, are not recognizable in outline—explaining in part why the blind can understand most line drawings made by sighted people. In the picture of the author on the left, a single contour separates the light and dark areas of his face. In the picture on the right, a line, having two contours, makes the same division. Note that although the shapes are identical in both images, the perceptual results are quite different. Only the image on the left clearly resembles a face.

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MORE TO EXPLORE

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Phantom LIMBS

People who have lost an arm or a leg often perceive the limb as though it were still there. Treating the pain of these ghostly appendages remains difficult

BY RONALD MELZACK

In 1866 S. Weir Mitchell, the foremost American neurologist of his time, published his first account of phantom limbs, not in a scientific journal but in the *Atlantic Monthly,* as an anonymously written short story. In his tale, "The Case of George Dedlow," the protagonist loses an arm to amputation during the Civil War. Later, he awakens in the hospital after, unbeknownst to him, both his legs have also been amputated.

> [I was] suddenly aware of a sharp cramp in my left leg. I tried to get at it … with my single arm, but, finding myself too weak, hailed an attendant. "Just rub my left calf,… if you please."
> "Calf?… You ain't got none, pardner. It's took off."

Some historians have speculated that Mitchell chose to publish in the *Atlantic* as a way of testing the reaction of his peers to the concept of phantom limbs. He feared they would not believe amputated arms and legs could be felt after the limbs were gone.

In fact, the phenomenon of phantom limbs is common. So is the occurrence of terrible pain in these invisible appendages. Yet neither the cause of phantoms nor the associated suffering is well understood. My colleagues and I have proposed explanations that are leading to fresh research into treatments for the often intractable pain. The concepts also raise questions about basic assumptions of contemporary psychology and neuroscience.

The most extraordinary feature of phantoms is their reality to the amputee. Their vivid sensory qualities and precise location in space—especially at first—make the limbs seem so lifelike that a patient may try to step off a bed onto a phantom foot or lift a cup with a phantom hand. The phantom, in fact, may seem more substantial than an actual limb, particularly if it hurts.

In most cases, a phantom arm hangs straight down at the side when the person sits or stands, but it moves in perfect coordination with other limbs during walking—that is, it behaves like a normal limb. Similarly, a phantom leg bends as it should when its owner sits; it stretches out when the individual lies down; and it becomes upright during standing.

Sometimes, however, the amputee is sure the limb is stuck in some unusual position. One man felt that his phantom arm extended straight out from the shoulder, at a right angle to the body. He therefore turned sideways whenever he passed through doorways, to avoid hitting the wall. Another man, whose phantom arm was bent behind him, slept only on his abdomen or on his side because the phantom got in the way when he tried to rest on his back.

The eerie reality of phantoms is often reinforced by sensations that mimic feelings in the limb before amputation. For example, a person may feel a painful ulcer or bunion that had been on a foot or even a tight ring that had been on a finger. Such individuals are not merely recollecting sensations but are feeling them with the full intensity and detail of an ongoing

A missing arm or leg is often perceived as perfectly real to the patient, who describes it as being in various positions and often reports feeling pain in it.

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experience. The reality of the phantom is also enhanced by wearing an artificial arm or leg; the phantom usually fills the prosthesis as a hand fits a glove.

The sense of reality is also strengthened by the wide range of sensations a phantom limb can have. Pressure, warmth, cold and many different kinds of pain are common. A phantom can feel wet (as when an artificial foot is seen stepping into a puddle). Or it can itch, which can be extremely distressing, although scratching the apparent site of discomfort can sometimes actually relieve the annoyance. The person may also feel as if the limb is being tickled or is sweaty or prickly.

Naturally, of all the sensations in phantom limbs, pain, which as many as 70 percent of amputees suffer, is the most frightening and disturbing. It is often described as burning, cramping or shooting and can vary from being occasional and mild to continuous and severe. It usually starts shortly after amputation but sometimes appears weeks, months or years later. A typical complaint is that a hand is clenched, fingers bent over the thumb and digging into the palm, so that the whole hand is tired and achy. In the leg the discomfort may be felt as a cramp in the calf. Many patients report that their toes feel as if they are being seared by a red-hot poker.

A final striking feature of phantoms, which reinforces the reality still further, is that they are experienced as a part of oneself. That is, patients perceive them as integral parts of the body. A phantom foot is described not only as real but as unquestionably belonging to the person. Even when the foot is felt to be dangling in the air several inches beneath the stump and unconnected to the leg, it is still experienced as part of one's body, and it moves appropriately with the other limbs and with the torso.

Amputation is not essential for the occurrence of a phantom. In some accidents, particularly when a rider is thrown off a motorcycle and hits the pavement, the shoulder is wrenched forward so that all the nerves from the arm are ripped from the spinal cord, a condition known as a brachial plexus avulsion. The resulting phantom occupies the now useless true arm and is usually coordinated with it. But if the victim's eyes are closed, the phantom will remain in its original position when the real arm is moved by someone else. Although the flesh-and-blood arm is incapable of responding to stimulation, the phantom version is usually extremely painful. Regrettably, even surgical removal of the true arm has no effect on the phantom or on the pain.

Similarly, paraplegics—persons who have had a complete break of the spinal cord and therefore have no feeling in, or control over, their body below the break—often have phantom legs and other body parts, including genitals. Immediately after an accident, the phantom may be dissociated from the real body. For instance, a person may feel as if the legs are raised over the chest or head even when he or she can see that they are stretched out on the road. Later, though, phantoms move in coordination with the body, at least when the person's eyes are open. Some paraplegics complain that their legs make continuous cycling movements, producing painful fatigue, even though a patient's actual legs are lying immobile on the bed. Phantoms are also reported by patients whose spinal cords are anesthetized, such as by a spinal block during labor.

The existence of **phantoms in people** born without a limb suggests that the neural networks for perceiving the body are built into the brain.

The oldest explanation for phantom limbs and their associated pain is that the remaining nerves in the stump, which grow at the cut end into nodules called neuromas, continue to generate impulses. The impulses flow up through the spinal cord and parts of the thalamus (which is a central way station in the brain) to the somatosensory areas of the cortex. These cortical areas are the presumed centers for sensation in classical concepts of the nervous system.

On the basis of this explanation, treatments for pain have attempted to halt the transmission of impulses at every level of the somatosensory projection system. The nerves from the stump have been cut, usually just above the neuroma or at the roots—small bundles of fibers that arise when the sensory nerves divide into smaller branches, just before they enter the spinal cord. Pathways within the spinal cord have been cut as well, and the areas of the thalamus and cortex that ultimately receive sensory information from the limb have been removed.

Although these approaches may provide relief for months or even years, the pain usually returns. Moreover, none of these procedures abolish the phantom limb itself. Hence, neuroma activity cannot by itself account either for the phenomenon of the phantom limb or for the suffering.

A related hypothesis moves the source of phantom limbs from neuromas to the spinal cord, suggesting that phantoms arise from excessive, spontaneous firing of spinal cord neurons that have lost their normal sensory input from the body. The output of the cells is transmitted to the cortex, just as if the spinal neurons had received external stimulation. This proposal grew in part out of research done in the 1960s showing that after sensory nerves in the body are cut, neurons in the spinal cord spontaneously generate a high level of electrical impulses, often in an abnormal, bursting pattern.

Other observations indicate that this explanation is insuf-

THE AUTHOR

RONALD MELZACK is professor emeritus of psychology at McGill University. His work on the neurophysiology of pain spans five decades. After obtaining his Ph.D. in psychology at McGill in 1954 and taking up fellowships in the U.S. and abroad, he joined the faculty of the Massachusetts Institute of Technology in 1959. There he and the late Patrick D. Wall began discussions that led to the publication in 1965 of their now famous gate control theory of pain. Melzack joined the McGill faculty in 1963.

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ficient. Paraplegics who have suffered a complete break of the spinal cord high in the upper body sometimes feel severe pain in the legs and groin. Yet the spinal neurons that carry messages from those areas to the brain originate well below the level of the break, which means that any nerve impulses arising in those neurons would not traverse the break.

More recent work has led to the proposal that phantom limbs can arise still higher in the central nervous system—in the brain itself. One hypothesis holds that phantoms are caused by changes in the flow of signals through the somatosensory circuit in the brain.

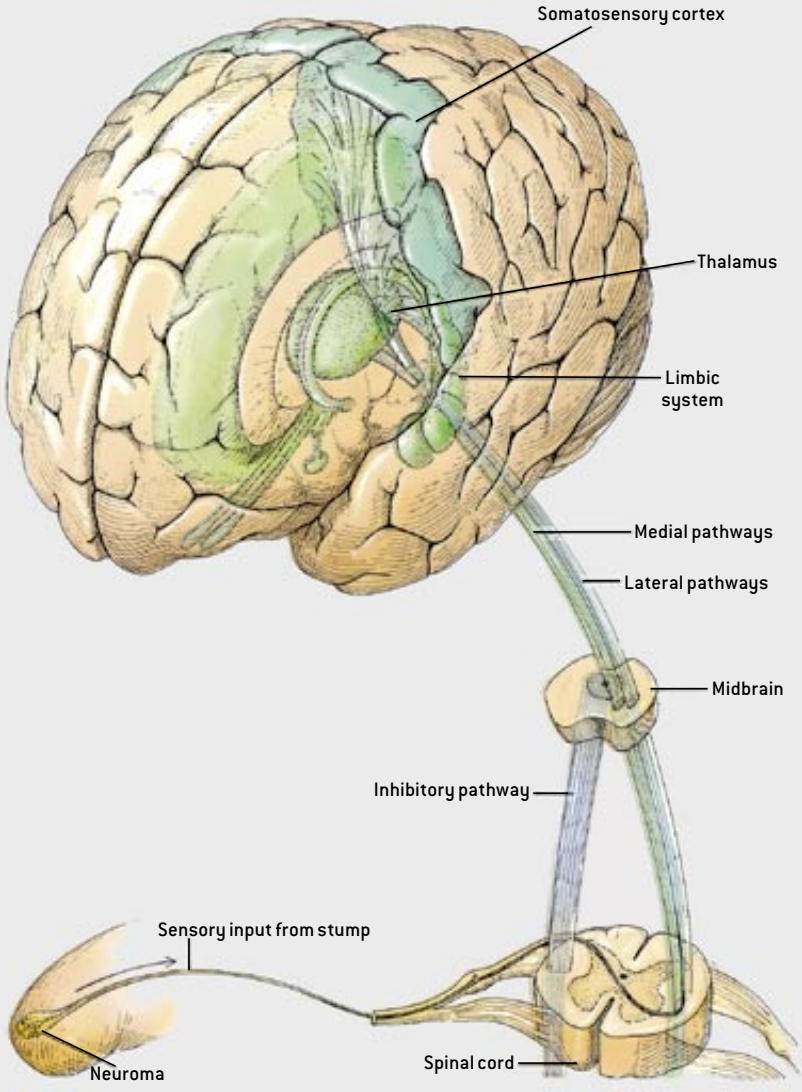
For example, Frederick A. Lenz, then at the University of Toronto, observed abnormally high levels of activity and a bursting pattern in cells of the thalamus in a paraplegic patient who had a full break of the spinal cord just below the neck but nonetheless suffered pain in the lower half of his body. The overactive cells, it turned out, also responded to touches of the head and neck, even though the cells were in the area of the thalamus that normally responds only to stimulation of the body below the level of the cut. This finding suggested that neural inhibition was lifted on the flow of signals across existing but previously unused synapses in sensory neurons projecting to the thalamus from the head and neck.

Such changes in the somatosensory thalamus or cortex could help explain why certain feelings arise in limbs that no longer exist or can no longer transmit signals to the brain. Nevertheless, alterations in this system cannot by themselves account for phantoms and their pain. If this explanation were sufficient, removal of the affected parts of the somatosensory cortex or thalamus would solve both problems.

Clearly, the source of phantom limbs is more complex than any of these theories would suggest. No other hypotheses have been proposed, however. As an outgrowth of my interest in the brain mechanisms that give rise to pain, I have pondered the causes of phantoms and phantom-limb pain and studied patients with these problems for many years.

Signaling the Brain

Pathways of signals from the body to the brain are shown. After the loss of a limb, nerve cells in the denervated areas of the spinal cord and brain fire spontaneously at high levels and with abnormal bursting patterns.



Self-Awareness Neuromatrix

MY WORK AND THAT OF OTHERS have led me to conclude that, to a great extent, phantom limbs originate in the brain, as the work of Lenz would suggest. But much more of the cerebrum than the somatosensory system is involved.

Any explanation must account for the rich variety of sensations a person can feel, the intense reality of the phantom and the conviction that even free-floating phantoms belong to the self. I have proposed such a model. It has been well received, but it must, of course, be tested more fully before its value can be assessed completely. Meanwhile, though, it has already generated new ideas for research into stopping the pain that arises from phantom limbs.

In essence, I postulate that the brain contains a neuromatrix, or network of neurons, that, in addition to responding to sensory stimulation, continuously generates a characteristic pattern of impulses indicating that the body is intact and unequivocally one's own. I have called this pattern a neurosignature. If such a matrix operated in the absence of sensory in-

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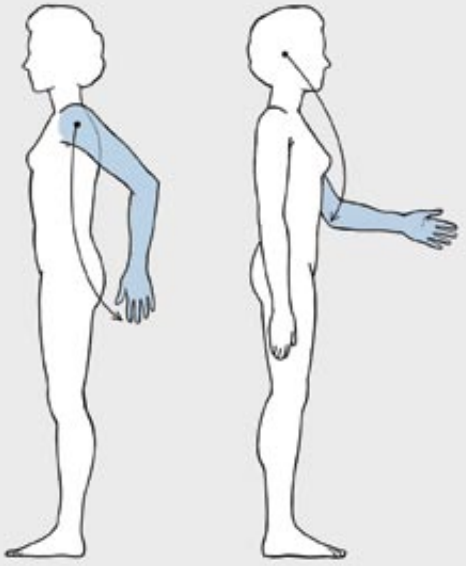
Projected Pain



Referred sensations in a painful phantom arm were reported by a woman receiving electric stimuli at two points (*dots*). Stimulation at the stump gave the sensation of electric shocks that jumped from finger to finger. Stimulation on the right ear made the left phantom elbow feel warm and caused a pulsation that traveled down the phantom wrist and thumb. The observations were made by Joel Katz, now at the University of Toronto, and the author.

puts from the periphery of the body, it would create the impression of having a limb even after that limb has been removed.

To produce all the qualities I have described for phantoms, the matrix would have to be quite extensive, including at least three major neural circuits in the brain. One of them, of course, is the classical sensory pathway passing through the thalamus to the somatosensory cortex. A second system must consist of the pathways leading through the reticular formation of the brain stem to the limbic system, which is critical for emotion and motivation. I include this circuit in part because I and others have noted that paraplegics who suffer a complete spinal break high in the upper body continue to experience themselves as still being in their old body, and they describe the feelings in the denervated areas with the same kinds of affective terms as they did before they were injured, such as "painful," "pleasurable" or "exhausting."

A final system consists of cortical regions important to recognition of the self and to the evaluation of sensory signals. A major part of this system is the parietal lobe, which in studies of brain-damaged patients has been shown to be essential to the sense of self.

Indeed, patients who have suffered a lesion of the parietal lobe in one hemisphere have been known to push one of their own legs out of a hospital bed because they were convinced it belonged to a stranger. Such behavior shows that the damaged area normally imparts a signal that says, "This is my body; it is a part of my self."

I believe that when sensory signals from the periphery or elsewhere reach the brain, they pass through each of these systems in parallel. As the signals are analyzed, information about them is shared among the three systems and converted into an integrated output, which is sent to other parts of the brain. Somewhere in the brain the output is transformed into a conscious perception, although no one knows exactly where the transformation that leads to awareness takes place.

As dynamic as this description may seem, the processing is probably still more dynamic than that. I further propose that as the matrix analyzes sensory information, it imprints its characteristic neurosignature on the output. Thus, the output carries information about sensory input as well as the assurance that the sensation is occurring in one's own body. The neurosignature may be likened to the basic theme of an orchestral piece. The collective sound changes when different instruments play their parts (the input), but the product is continually shaped by the underlying theme (the neurosignature), which provides the continuity for the work, even as the details of its rendition change.

Genetically Prewired Matrix

THE SPECIFIC NEUROSIGNATURE of an individual would be determined by the pattern of connectivity among neurons in the matrix—that is, by such factors as which neurons are connected to one another and by the number, types and strengths of the synapses. Readers familiar with neuroscience will note that my conception of the neuromatrix has similarities to the notion of the cell assembly proposed long ago by Donald O. Hebb of McGill University. Hebb argued that when sensory input activates two brain cells simultaneously, synapses between the cells form stronger connections. Eventually the process gives rise to whole assemblies of linked neurons, so that a signal going into one part of an assembly spreads through the rest, even if the assembly extends across broad areas of the brain.

I depart from Hebb, however, in that I visualize the neuromatrix as an assembly whose connections are primarily determined not by experience but by the genes. The matrix, though, could later be sculpted by experience, which would add or delete, strengthen or weaken, existing synapses. For instance, experience would enable the matrix to store the memory of a pain from a gangrenous ulcer and might thus account for the frequent reappearance of the same pain in phantom limbs.

I think the matrix is largely prewired, for the simple reason that my students and I have encountered many people who were born without an arm or a leg and yet experience a vivid phantom. For example, a 32-year-old engineer who was born without a leg below the knee reports that his phantom leg and foot remain vivid but vanish for several hours once or twice a week. He reports that he is always delighted when they return.

Similarly, Peter Brugger and his colleagues at University Hospital Zürich describe a 44-year-old woman born without forearms and legs who had vivid phantoms of all four limbs since childhood. Imaging (fMRI) studies of her brain while she made complex movements with her phantom hands showed activity in her premotor and parietal cortex (an area strongly associated with our sense of self). In another study,

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transcranial magnetic stimulation of the sensorimotor cortex consistently elicited sensations in her contralateral phantom fingers and hand. Clearly, the brain's substrates for phantom limbs are in place where they should be even though physical limbs never existed.

The powerful sense of reality of phantom limbs is evident in the classic explanation by an 11-year-old girl—born without forearms or hands but with vivid phantom hands—of the way she learned to do simple arithmetic at school: She placed her phantom hands on her desk and counted on her outstretched phantom fingers!

Parenthetically, I should note that the long-held belief that phantoms are experienced only when an amputation has occurred after the age of six or seven is not true. My postdoctoral student Renée Lacroix and I confirmed earlier reports that children who lose a limb when they are as young as one or two years old can have phantom limbs. We have also encountered children who have painful phantoms of legs that were lost before age two.

Under normal circumstances, then, the myriad qualities of sensation people experience emerge from variations in sensory input. This input is both analyzed and shaped into complex experiences of sensation and self by the largely prewired neuromatrix. Yet even in the absence of external stimuli, much the same range of experiences can be generated by other signals passing through the neuromatrix—such as those produced by the spontaneous firing of neurons in the matrix itself or the spinal cord or produced by neuromas. Regardless of the source of the input to the matrix, the result would be the same: rapid spread of the signals throughout the matrix and perception of a limb that is located within a unitary self, even when the actual limb is gone.

The fading of phantom limbs and their pain, which sometimes occurs over time, would be explained if cerebral neurons that once responded to lost or paralyzed limbs develop increasingly strong connections with still sensate parts of the body and then begin to serve those regions. In the process the neurosignature pattern would change, resulting in changes in the phantom and the pain. But phantoms do not usually disappear forever. In fact, they may return decades after they seem to have gone, which indicates that the neuromatrix, even when modified, retains many of its features permanently.

My students Anthony L. Vaccarino, John E. McKenna and Terence J. Coderre and I gathered some direct evidence supporting my suggestion that the brain—and by implication, the neuromatrix—can generate sensation on its own. Our studies relied on what is called the formalin pain test.

We injected a dilute solution of formalin (formaldehyde dissolved in water) under the skin of a rat's paw, which produces pain that rapidly rises and falls in intensity during the first five minutes after the injection. (The degree and duration of discomfort are assessed by such behaviors as licking the paw.) This "early" response is followed by "late" pain, which begins about 15 minutes after the injection and persists for about an hour.

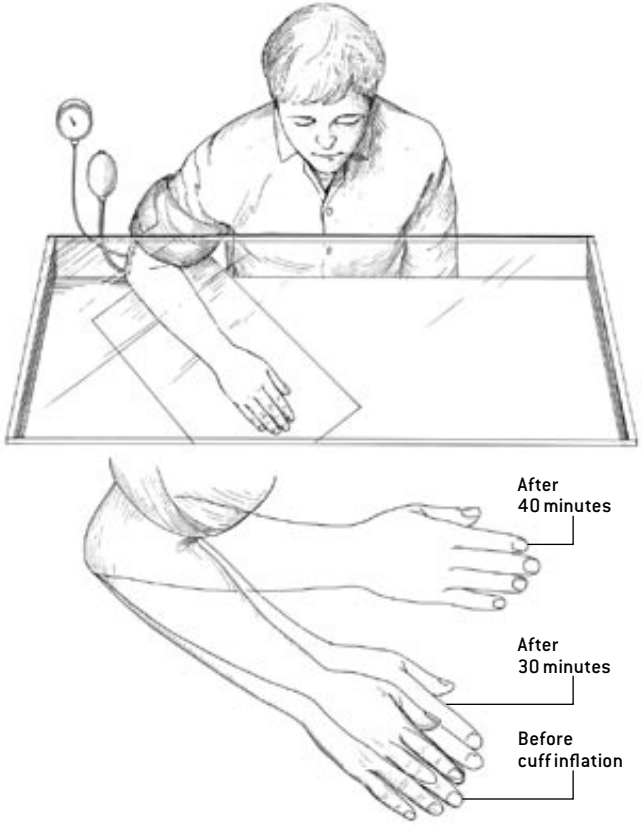
By means of this test, we found that an anesthetic block of the paw completely obliterates the late pain but only if the anesthetic is delivered in time to prevent the early response. Once the early pain occurs, the drug only partly reduces the later response. This observation of pain continuing even after the nerves carrying pain signals are blocked implies that long-lasting pain (such as that in phantoms) is determined not only by sensory stimulation during the discomfort but also by brain processes that persist without continual priming.

Phantom-Limb Pain

BUT WHAT EXACTLY causes the pain in phantom limbs? The most common complaint is a burning sensation. This feeling could stem from the loss of sensory signaling from the limb to the neuromatrix. Without its usual sensory stim-

Perception vs. Reality

A real arm made insensate by an inflated pressure cuff resembles a phantom arm. The subject could not see the arm, because the table was covered by a black cloth. The positions of the hand felt before the cuff was inflated and at intervals thereafter, as the hand seemed to be closer to the body, are shown. This study was carried out with Yigal Gross, now at Bar-Ilan University in Israel.



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ulation, the neuromatrix would probably produce high levels of activity in a bursting pattern, such as Lenz observed in the thalamus. This kind of signal may very well be transformed into an awareness of burning.

Other pain may result from the effort of the neuromatrix to make the limbs move as they normally would. When the limbs do not respond in amputees and paraplegics, the neuromatrix (which would be prewired to "assume" the limbs can indeed move) may issue more frequent and stronger messages urging the muscles to move the limb. These outputs may be perceived as cramping. Similar output messages might also be felt as shooting pain.

Research to test some of these ideas and explore new ways of eliminating pain is still in its infancy, but some intriguing results are beginning to emerge. The need for such treatments is urgent, both because the suffering can be severe and persistent and because, sadly, few methods are permanently effective.

At the moment, a number of different therapies are used. Stimulation of the stump with electric currents, a vibrator or acupuncture helps some amputees. Relaxation and hypnosis aid others. Some individuals obtain considerable relief from drugs that are usually given to counteract epilepsy or depression, and other patients find their pain is eased by a combination of an antidepressant and a narcotic (such as methadone). But about half of those with persistent, long-term phantom pain fail to respond to any approach.

Phantom-limb pain highlights the differences between two major kinds of pain. The first is pain related to a specifiable injury or disease, which stimulates specialized somatic receptors and spinal pathways to the somatosensory cortex. The second is severe chronic pain, which is usually out of proportion to an injury or other pathology and persists long after healing is complete. Facial and postherpetic neuralgia, pelvic and urogenital pain, most back pains and headaches, and fibromyalgia are among a long list of chronic pains that have no apparent cause and defy drugs and therapies. The evidence that excruciating pain may be felt in the phantom half of the body after a total break in the spinal cord tells us that the brain does more than detect and analyze sensory inputs; it creates perceptual experience even in the absence of external inputs. We do not need a body to feel a body or a physical injury to feel pain.

Phantom Seeing and Hearing

Like phantom limbs, phantom seeing and hearing are also generated by the brain in the absence of sensory input. People whose vision has been impaired by cataracts or by the loss of a part of the visual processing system in the brain sometimes report highly detailed visual experiences. This syndrome was first described in 1769, when philosopher Charles Bonnet wrote an article on the remarkable visual experiences of his grandfather, Charles Lullin, who had lost most of his vision because of cataracts but was otherwise in good physical and psychological health. Since then, many mentally sound individuals have reported similarly vivid phantom visual experiences.

Phantom seeing often coexists with a limited amount of normal vision. The person experiencing the phantom has no difficulty in differentiating between the two kinds of vision. Phantom visual episodes appear suddenly and unexpectedly when the eyes are open. People usually describe the visual phantoms as seeming real despite the obvious impossibility of their existence. Common phantom images include people and large buildings. Rarer perceptions include miniature people and small animals. Phantom sights are not mere memories of earlier experiences; they often contain events, places or people that have never before been encountered.

First appearances of phantom images can be quite startling. A woman in one of our studies who had lost much of her vision because of retinal degeneration reported being shocked when she looked out a window and saw a tall building in what she knew to be a wooded field. Even though she realized that the building was a phantom, it seemed so real that she could count its steps and describe its other details. The building soon disappeared, only to return several hours later. The phantom vision continues to come and go unexpectedly, she explained to my student Geoffrey Schultz.

Phantom seeing occurs most among the elderly, presumably because vision tends to deteriorate with age. Some 15 percent of those who lose all or part of their vision report phantom visual experiences. The proportion may be higher because some people avoid discussing phantom vision for fear of being labeled as psychologically disturbed.

Phantom sounds are also extremely common, although few people recognize them for what they are. Those who lose their hearing commonly report noises in their heads. These noises, called tinnitus, are said to sound like whistling, clanging, screeching or the roaring of a train. They can be so loud and unpleasant that the victim needs help to cope with the distress they cause.

Some individuals with tinnitus report hearing "formed sounds," such as music or voices. A woman who had been a musician before losing her hearing says she "hears" piano concertos and sonatas. The impression is so real that at first she thought the sounds were coming from a neighbor's radio. The woman reports that she cannot turn off the music and that it often gets louder at night when she wants to go to sleep. Another woman, who had lost much of her sight and hearing, experienced both phantom sight and sound. In one instance, she described seeing a circus and hearing the music that accompanied the acts.

Phantom sights and sounds, like phantom limbs, occur when the brain loses its normal input from a sensory system. In the absence of input, cells in the central nervous system become more active. The brain's intrinsic mechanisms transform that neuronal activity into meaningful experiences. —*R.M.*

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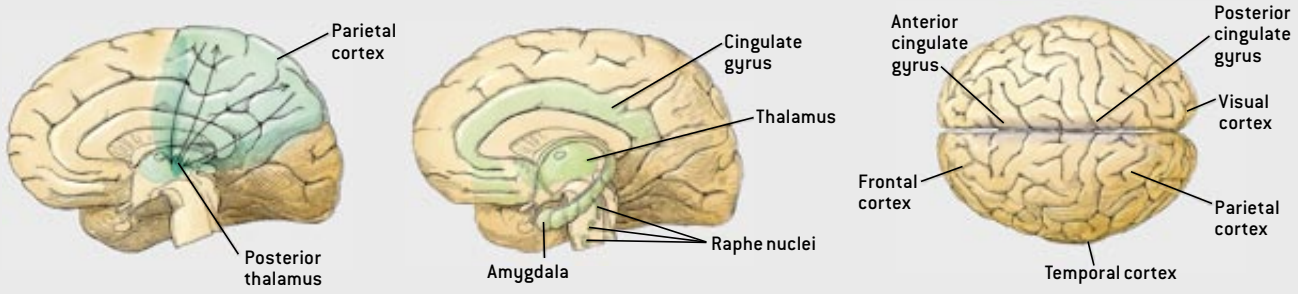
All in Your Head

The source of phantom limbs is thought by the author to involve activity in three of the brain's neural circuits. One of them (*left*) is the somatosensory receiving areas and the adjacent parietal cortex, which process information related to the body. The second (*center*) is the limbic system, which is concerned with emotion and motivation. The third (*right*) encompasses the widespread cortical networks involved in cognitive activities, among them memory of past experience and evaluation of sensory inputs in relation to the self.



The depiction of pain as a simple, straight-through neural transmission system, as shown on page 55, requires further consideration. The transmission of messages to the brain represents only stage 1 of the larger conceptual scheme for pain. Stage 2 is the much more extraordinary transformation of the nerve messages into conscious experience within the brain. René Descartes, in 1664, ascribed the transformation to a nonphysical mind (or soul) that resides in the central part of the brain. In the 21st century the challenge to scientists is to discover what happens in the brain during stage 2. *How* are nerve impulses transformed into the conscious experience of pain? The key to abolishing phantom-limb pain and all other chronic pains lies within the brain.

Because my model of brain functioning posits that the neuromatrix as a whole may contribute to pain, the model also suggests that altering the activity of pathways outside the somatosensory system might be important, either alone or in combination with other treatments. One place to begin work is the limbic system. Until recently, limbic structures have been relegated to a secondary role in efforts to treat pain. Nevertheless, if the limbic system contributes to output by the neuromatrix, as I have proposed, it might well contribute to the pain felt in phantom limbs.

Vaccarino, McKenna, Coderre and I have done work that tests the value of manipulating the limbic system as a way of easing pain. We have shown that localized injection of lidocaine (a relative of cocaine that prevents neurons from transmitting signals) into diverse areas of the limbic system produces striking decreases in several types of experimentally produced pain in rats, including a model of phantom-limb pain. A similar approach could be feasible for relieving phantom-limb pain in humans but needs more study.

The phenomenon of phantom limbs is more than a challenge to medical management. It raises doubts about some fundamental assumptions in psychology. One such assumption is that sensations are produced only by stimuli and that perceptions in the absence of stimuli are psychologically abnormal. Yet phantom limbs, as well as phantom seeing and hearing, indicate this notion is wrong.

The Brain's Body Image

ANOTHER ENTRENCHED ASSUMPTION is that perception of one's body results from sensory inputs that leave a memory in the brain; the total of these signals becomes the body image. But the existence of phantoms in people born without a limb or who have lost a limb at an early age suggests that the neural networks for perceiving the body and its parts are built into the brain. The absence of inputs does not stop the networks from generating messages about missing body parts; they continue to produce such messages throughout life.

In short, phantom limbs are a mystery only if we assume the body sends sensory messages to a passively receiving brain. Phantom limbs become comprehensible once we recognize that the brain generates the experience of the body. Sensory inputs merely modulate that experience; they do not directly cause it. A new generation of scientists will, I hope, face the brain head-on and discover how these events occur. SA

MORE TO EXPLORE

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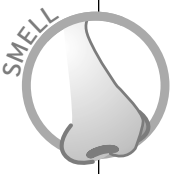

Are you ready for a NEW SENSATION?

As biology meets engineering, scientists are designing the sensory experiences of a new tomorrow

BY KATHRYN S. BROWN

The flimsy strip of golden film lying on John Wyatt's desk looks more like a candy wrapper than something you would willingly put in your eye. Blow on it, and the two-millimeter foil curls like cellophane. Rub it, and the shiny film squeaks faintly between your fingers. In fact, you have to peer rather closely to spot a neat patchwork: a tiny photodiode array, designed to bypass damaged cells in a retina and, Wyatt hopes, allow the blind to see.

This small solar panel is part of a prototype retinal implant. For more than 15 years, Wyatt—an engineer at the Massachusetts Institute of Technology—and his colleagues have pursued an implant to electrically stimulate the retina. At first, even Wyatt doubted the project could succeed. The retina, he says, is more fragile than a wet Kleenex: it is a quarter of a millimeter thin and prone to tearing. In about 10 million

continued on page 64

NICOLE ROSENTHAL

The buzz of a bee, the stripes of a butterfly, the perfume of a rose, the taste of a berry. It's all in the senses, and scientists are now onto how they work.

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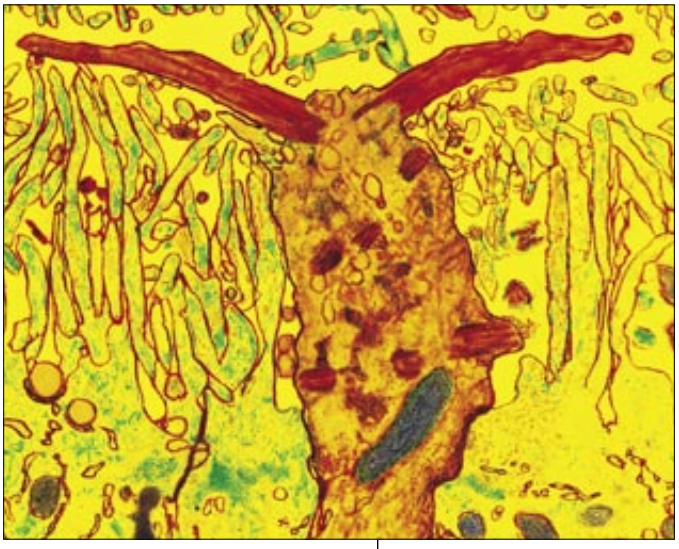
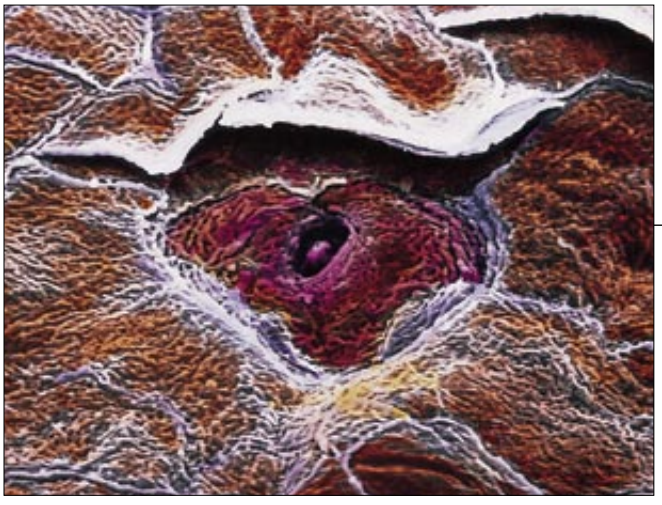
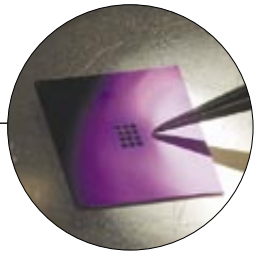


If someone tells you to wake up and smell the coffee, he or she might want you to use one of these. This orange blob is one of the thousands of olfactory receptors that make up the olfactory epithelium, a patch of mucous membrane way up in the nose that helps you sniff whether your milk has turned (among other things). Researchers have mimicked a dog's nose, which is even more sensitive than a human's, with an artificial nose (*below*) that can be used by companies to sniff for toxins.





No, this isn't a close-up of one of those nubbly things on the surface of your tongue. Those are papillae; this is the opening of a taste bud. Hundreds of these barrel-shaped structures (*seen here from above*) are embedded in some types of papillae. When flavors enter the tiny pore in the center, they bind to and react with molecules called receptors on the surface of each of the taste cells, which make up the staves of the barrel. Scientists aren't producing an implantable artificial tongue just yet, but they have designed a "taste chip" (*right*) that could be used to check the quality of wine or the purity of water.

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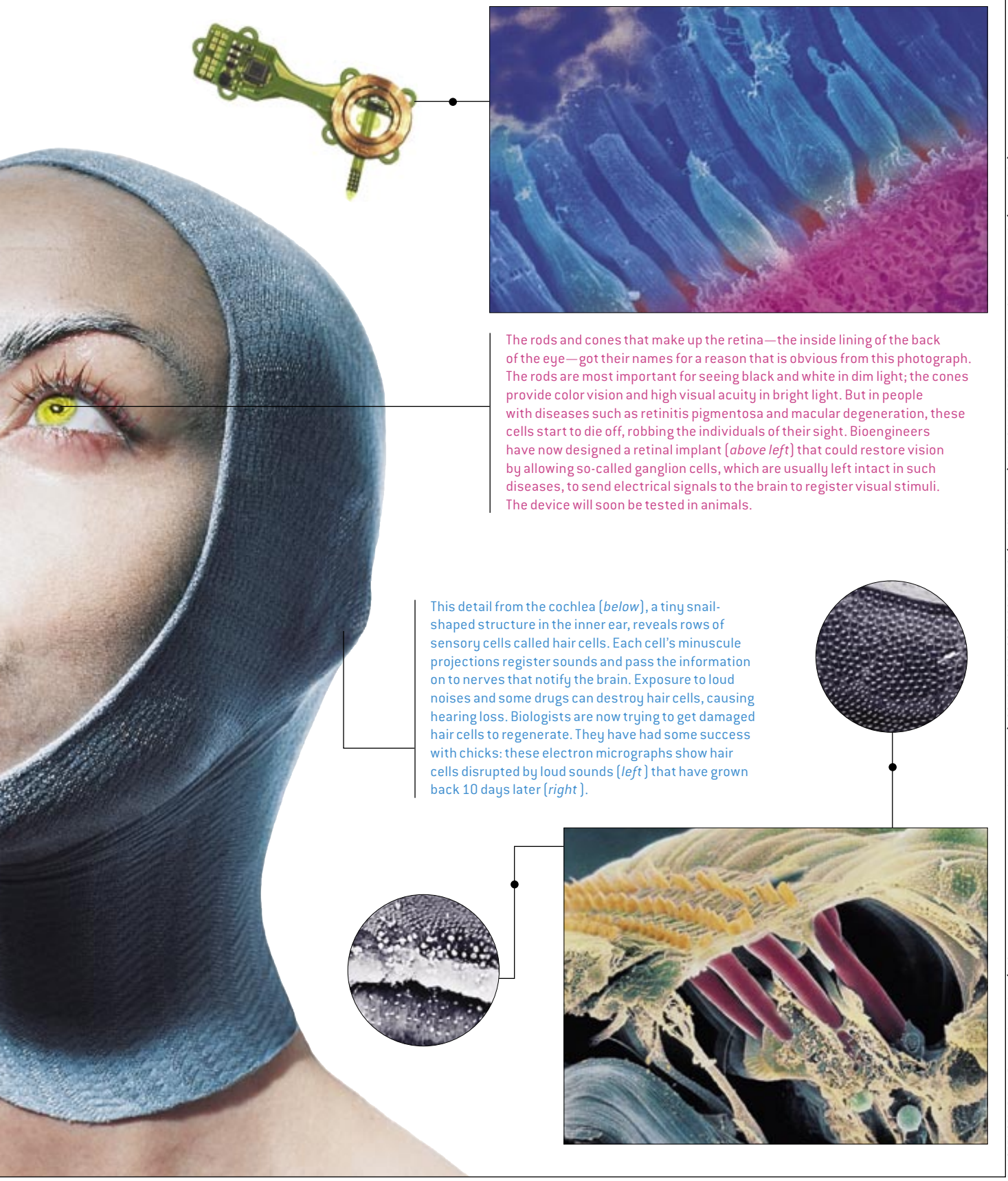

The rods and cones that make up the retina—the inside lining of the back of the eye—got their names for a reason that is obvious from this photograph. The rods are most important for seeing black and white in dim light; the cones provide color vision and high visual acuity in bright light. But in people with diseases such as retinitis pigmentosa and macular degeneration, these cells start to die off, robbing the individuals of their sight. Bioengineers have now designed a retinal implant (*above left*) that could restore vision by allowing so-called ganglion cells, which are usually left intact in such diseases, to send electrical signals to the brain to register visual stimuli. The device will soon be tested in animals.

This detail from the cochlea (*below*), a tiny snail-shaped structure in the inner ear, reveals rows of sensory cells called hair cells. Each cell's minuscule projections register sounds and pass the information on to nerves that notify the brain. Exposure to loud noises and some drugs can destroy hair cells, causing hearing loss. Biologists are now trying to get damaged hair cells to regenerate. They have had some success with chicks: these electron micrographs show hair cells disrupted by loud sounds (*left*) that have grown back 10 days later (*right*).

P. MOTTA *SPL/Photo Researchers, Inc.* (*olfactory receptor and taste bud micrographs*); COURTESY OF COGNISCENT, INC. (*artificial nose*); MARSHA MILLER *University of Texas at Austin* (*taste chip*); ZACH GOLD (*woman*); PHOTO RESEARCHERS, INC. (*retinal micrograph*); BOSTON RETINAL IMPLANT PROJECT (*retinal implant*); SPL/PHOTO RESEARCHERS, INC. (*cochlea micrograph*); JEFFREY T. CORWIN AND DOUGLAS A. COTANCHE *University of Virginia*, REPRINTED WITH PERMISSION FROM *SCIENCE*, VOL. 240, PAGES 1772–1774, © 1988, AAAS (*hair cell micrographs*)

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continued from page 61

Americans—those with the disorders retinitis pigmentosa and macular degeneration—the delicate rod and cone cells lining the retina's farthest edges die, although ganglion cells closer to the lens in the center survive. In 1988 Harvard Medical School neuro-ophthalmologist Joseph Rizzo asked Wyatt two key questions: Could scientists use electricity to jolt these leftover ganglion cells and force them to perceive images? Could they, in effect, engineer an electronic retina?

They decided to try. Today Wyatt and Rizzo are perfecting their second implant prototype, a subretinal device that processes images viewed through a tiny camera mounted on special eyeglasses. Supported principally by the U.S. Department of Veterans Affairs, their team—known as the Boston Retinal Implant Project—plans to begin testing the implant in animals soon. Wyatt calls the project a "classic case of science: 10 seconds of brilliance followed by 10 years of dogged work."

A realist, Wyatt compares vision via retinal implants to playing the piano with boxing gloves. "Despite the best of scientific advances, our instruments remain crude, and the nervous system is very refined," he says. A truly noninvasive subretinal implant, commercially available widely to people the world over, remains a dot on the horizon.

Still, that horizon beckons—and Wyatt is not the only sensory scientist marching toward it. In the coming years, if scientific dreams become reality, we will see even when our eyes are damaged, taste sweet foods with less sugar, hear even when our ears grow old. As a bonus, we will have electronic noses to sniff out environments and taste chips to diagnose disease [*see box on opposite page*].

Researchers are increasingly discovering the powerful yin-and-yang of engineering and biology, says neuroscientist John S. Kauer of Tufts University, who is developing an electronic nose. "We start with biology and use mathematical or computer modeling as the basis for building an engineering device," Kauer explains. "That sparks questions relevant to biology, and around we go. Engineering informs biology, and vice versa."

We will see when our eyes are damaged, hear when our ears grow old, taste a much sweeter world.

Sweet Sensations

TO SOME, the blend of biology and engineering holds the allure of sweet success. For decades, a few companies have poured, tasted and tinkered with promising artificial sweeteners to rival sugar. The sweetener market has big potential. This year the average American will consume an estimated 140 pounds of pure cane sugar, corn syrup and other natural sweeteners. Today's most popular artificial sweeteners include aspartame (used in Equal), sucralose (in Splenda) and saccharine (in Sweet'N Low).

But if companies could just find the perfect formula for a fake sweetener—an elusive chemical concoction to give a bright, clear and brief sugary taste, stable when stirred into coffee or baked into cake—they could make a mint. What is more, corporate spokespeople hasten to note, this iconic artificial sweetener could significantly cut the calorie content of the average American diet.

That's where biology comes in. Over the past six years several teams of researchers—at the University of California, San Diego; the National Institutes of Health; Harvard University; the Monell Chemical Senses Center in Philadelphia; and elsewhere—have identified and characterized major cell receptors on the human tongue required for us to taste sweet, bitter and savory (umami) flavors. (Salty and sour flavors remain a molecular mystery.)

"We've used several molecular genetic approaches to prove that the cells expressing sweet and bitter responses are highly selectively tuned to respond only to attractive or aversive stimuli, respectively, and are hardwired to trigger appropriate behavioral responses," says Nicholas J. P. Ryba of the National Institute of Dental and Craniofacial Research, whose team worked with U.C.S.D. molecular biologist Charles S. Zuker's group on some of the pivotal taste cell studies.

Ryba and Zuker studied RNA sequences from the tongue to reveal likely genes for taste receptor cells. Next they bred "knockout" mice missing these putative genes and tested the mutants for telltale changes in taste. Finally, they homed in on specific cell receptors responsible for a mouse's ability to taste certain flavors. In this fashion, the team has, over the past five years, found a family of roughly 30 bitter receptors, one major sweet receptor and one major savory receptor.

What scientists have documented is simple: both mouse and man are suckers for taste—we lap up the sweet and avoid the bitter. From an evolutionary standpoint, this culinary bias keeps us from eating bitter poisons or foul food. On the downside, it can also make us fat.

To capitalize on these finds, Zuker in 1998 teamed with a group of scientists and businesspeople to launch Senomyx, a La Jolla, Calif.–based bio-

THE AUTHOR

KATHRYN S. BROWN is a science writer based in Alexandria, Va. She is principal of EndPoint Creative, LLC, and serves on the board of the D.C. Science Writers Association. She would use an e-nose to stop and smell the roses (or lavender) and an e-tongue to savor even more dark chocolate.

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An E-World of Sensing

As bioengineering gets sensual, the results go beyond our own bodies. Some researchers have developed electronic noses and taste chips, putting sensation to work. These mechanical versions of us promise to identify chemical weapons, monitor environments and detect infectious disease, among other uses.

John S. Kauer, a neuroscientist at Tufts University, has been studying the olfactory system for more than 30 years. And he has sniffed out an opportunity. In 2002 Kauer, along with Tufts neuroscientist Joel White and several others, founded a small company, CogniScent in North Grafton, Mass., to develop an artificial nose.

Unlike your nose, this variety is yellow, about the size of a half-gallon milk bottle, and resembles a door handle plate with a small screen in the middle. The nose's core technology, called ScenTraK, uses an array of optically activated sensors designed to turn color when exposed to certain compounds. Kauer and White based the nose on the olfactory properties of a superior sniffer: the dog. Just as a mutt takes repeated, rapid sniffs of its environment, so does the e-nose. When it detects a targeted compound, the nose's small screen lights up with a specific color.

Kauer envisions different noses for different uses. This fall, for instance, CogniScent plans to release ScenTaur, a nose designed to sniff out the volatile organic compounds released by mold in the indoor environment. To create ScenTaur, the company began by isolating signature chemicals within the mold compounds, such as alcohol and ketones. Then they engineered fluorescent DNA polymers that change color in the presence of those compounds.

"We've built a core sensory module that we think can be altered into one device that detects mold, another that can diagnose disease, another for environmental monitoring of chemical weapons, and so on," Kauer says, adding that CogniScent is currently supported by grants from the Department of Homeland Security. "We hope to make strategic alliances with other companies that can apply the technology."

They are not alone. Among other ventures, Pine Brook, N.J.–based Smiths Detection, an operating unit of Smiths Group, has devised several such handheld noses, including the TravelIR HazMat Chemical Identifier, used by emergency responders in 2002 to identify the white powder seeping from a boxed package at a Washington, D.C., post office. (It was infant formula.)

After a five-month trial period, the New York Metropolitan Transportation Authority announced this spring that it will use two other Smiths Detection devices to seek out explosives and identify foreign chemicals in and around the city's commuter rail system.

And why stop at sniffing? Electronics are now tasting, too. Chemist John T. McDevitt and his colleagues at the University of Texas at Austin pioneered the electronic "taste chip," an etched silicon wafer dotted with microreactors that can measure and quantify the ingredients in a complex fluid. That work has led to the development of a second chip, with a membrane filter and modified microfluidics that can trap and optically analyze fluids. For instance, given a patient's blood sample, the chip can count various immune cells to assess that patient's immune system function.

Since developing the taste chip, McDevitt has received phone calls from across the globe, both curious and corporate. Could it be used to taste wine? What about the safety of water? How might it be fully exploited as a viral assay? In the future, he says, the work might even come full circle, offering new ways to manipulate human taste. —*K.S.B.*

Electronic nose could be used to check for vapors of toxic industrial chemicals leaking from a pipe or valve, as shown in this simulation using CogniScent's ScenTraK prototype. Devices such as ScenTraK could also be used to detect hazardous chemicals after an accident or a terrorist attack.

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technology company working to develop novel flavor ingredients for packaged foods and drinks. With corporate partners such as Coca-Cola, Nestlé and Kraft, roughly 85 Senomyx scientists are closing in on a chemical compound known as a taste potentiator—a flavor booster that will allow companies to manufacture sweet-tasting foods with less sugar.

Now Hear This

RATHER THAN AMPLIFY sensory experience, neuroscientist Jeffrey T. Corwin of the University of Virginia hopes to re-create it—in the ear. Worldwide, an estimated 250 million people endure disabling hearing impairments, according to the World Health Organization. The major culprit is the permanent loss of sensory hair cells in the inner ear.

The inner ear is home to the pea-size cochlea, which holds some 16,000 sound-detecting cells, each of which is equipped with hairlike projections that have earned them the name "hair cells." This precious stock of cells is a gift at birth: they never multiply, but they do die. Loud noise, disease and just plain aging damage hair cells, muffling one's ability to hear sounds that once seemed crystal clear.

Scientists know that animals as diverse as zebra fish and chickens continue adding cells for hearing or balance throughout life. The adult shark has some 240,000 sensory cells in its inner ear, up from 20,000 in its younger days. Why not us? Biologically, human hair cells are held in a kind of "mitotic arrest"—shut down from cell division, so they cannot replicate.

One key protein that suspends the human hair cell's cycle is the retinoblastoma protein (pRb). This protein inhibits the expression of genes needed to kick-start cell division. And that can be good: pRb is thought to suppress the complex runaway cell growth that is cancer. But neuroscientists have long wondered whether they could effectively modulate pRb in the inner ear, essentially dimming the protein to allow hair cells to safely regenerate.

In an important first step, Corwin, together with Zheng-Yi Chen and colleagues at Harvard Medical School, Tufts–New England Medical Center and Northwestern University, recently found that shutting off pRb in mouse hair cells prompted those cells to divide and multiply. Most important, the new cells worked normally.

"There are solid scientific reasons to believe that we can develop a pharmaceutical that will encourage cell growth, production and regeneration," Corwin remarks. "That is the holy grail." Richard J. H. Smith, director of molecular otolaryngology at the University of Iowa, goes a step further: "One day we will be able to prevent hearing loss altogether."

In preliminary experiments, Smith and his colleagues have used a technique known as RNA interference, or RNAi, to silence a potential deafness gene in mice. He hopes this early work will eventually translate into gene therapy for patients with inherited progressive hearing loss. Although skeptics question whether gene therapy—or another hyped technique, the use of stem cells—can be reliably used as clinical treatment, Smith maintains that genetics offers a unique molecular window into hearing.

"Investigators have identified more than 40 specific genes that are essential for normal hearing function," Smith says. "For example, if a mutated protein has an abnormal function that results in hearing loss, by preventing that protein from being made, it should be possible to prevent the hearing loss."

In the meantime, conventional hearing treatments keep improving, Corwin adds. In particular, he notes advances with the cochlear implant, a surgically implanted set of tiny electrodes that stimulates inner-ear cells, basically to turn up life's volume. Today more than 100,000 people worldwide wear these roughly $50,000 implants. Although scientists agree it is impossible to re-create completely the complex workings of the human ear, they can improve the frequencies and fluidity of sounds heard through an implant. Duke University engineers, for instance, are using mathematical algorithms to develop sound-processing software that eventually may help implant wearers enjoy music again.

Challenges Ahead

RESEARCHERS are also developing better implants for the eye. M.I.T.'s Wyatt quips that the retina, which is sensitive to even the slightest pressure, doesn't welcome a brick of a microchip any more than you would like being ca-

"A chronic implant has to be removable in the future or good for life. That's a pretty high hurdle."

ressed by a bulldozer. In fact, he says, this machine-man combination is the real showstopper: "After the retinal implant works, and we prove them, and the surgeons are familiar with them, then the interesting story starts. It's not about the hardwiring. It's about how patients translate the images they see. How do we learn to speak the neural code? Just what sense can patients make of this visual data, months or years down the line? What is their visual reality?"

If Wyatt's retinal implant makes it to market, that reality should work like this: A patient who has received an implant will wear special glasses equipped with a miniature camera that captures images. The glasses will sport a small laser that receives the camera's pictures and converts the visual information

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NICOLE ROSENTHAL

into electrical signals that travel to the implant, surgically inserted just below the retina. The implant, in turn, will activate the retina's ganglion cells to pick up the sensation of the image coming in and convey it to the brain, where it will be perceived as vision.

If it sounds complicated, Wyatt comments drily, that's because it is. Their biggest challenge, he says, is "encapsulation," or waterproofing the retinal implant to last in the human eye for years. "A chronic implant has to be removable in the future or good for life," he points out. "That's a pretty high hurdle."

Wyatt's team is not the only one trying to jump it. Optobionics, a start-up company in Wheaton, Ill., is also developing a subretinal implant, called the artificial silicon retina (ASR). This self-contained microchip contains roughly 5,000 solar cells that convert light into an electrical signal similar to that normally produced by the retina's own photoreceptor cells. The solar cells stimulate the remaining functional cells, which process and send signals to the brain via the optic nerve.

Because the ASR does not have an outside power source, camera or other device, it may provide only moderate enhancement for people who still have some sight. Privately held Optobionics—co-founded by brothers ophthalmologist Alan Y. Chow and engineer Vincent Chow—completed the first FDA-approved clinical trials of a subretinal implant in 2002. Follow-up trials continue, with implants tested at the Wilmer Eye Institute of Johns Hopkins University, Emory University and Rush University. Since initially publishing trial results in 2004, however, the company has remained tight-lipped about ASR's efficacy, with no further peer-reviewed journal articles.

Other efforts to develop retinal implants are under way at Stanford University, the Kresge Eye Institute in Detroit and a German company called Retina Implant AG. In addition, the National Science Foundation has awarded the University of Southern California a national engineering research center for developing microelectronic devices that mimic lost neurological functions. U.S.C.'s Center for Biomimetic MicroElectronic Systems is devoting $17 million to three projects, including a retinal implant.

Despite the hype, bioengineering advances are not finger-snap miracles but rather the slow, steady progression of science. "No retinal implant will ever be perfect," Wyatt cautions. "Either the electrodes are too big, or the wrong cells get stimulated, or something. But you *can* make the sensory experience better. And we're firmly on that path." SA

MORE TO EXPLORE

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Boston Retinal Implant Project website: **www.bostonretinalimplant.org**

Senomyx Web site: **www.senomyx.com**

Lab on a Chip: **www.tastechip.com**

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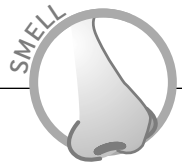

The molecular logic of SMELL

Mammals can recognize thousands of odors, some of which prompt powerful responses. Recent experiments illuminate how the nose and brain may perceive scents

BY RICHARD AXEL

Smell is perhaps our most evocative sense. In Marcel Proust's novel *Remembrance of Things Past,* the nostalgic flavor and fragrance of a madeleine, a delicate pastry, evokes a description of taste and smell, the senses that "alone, more fragile but more enduring, more unsubstantial, more persistent . . . bear unflinchingly, in the tiny and almost impalpable drop of their essence, the vast structure of recollection."

Humans often view smell as an aesthetic sense, yet for most animals smell is the primal sense, one they rely on to identify food, predators and mates. Indeed, for many organisms, odors are their most efficient means of communicating with others and interpreting their surroundings. Innate behavior in response to smell is essential to these organisms' survival and most likely results from nonconscious perception of odors.

Each individual has a unique, genetically determined scent. This olfactory identity is coupled with a remarkable ability to distinguish a diversity of odors. Humans, for instance, can recognize approximately 10,000 scents, ranging from the pleasurable scent of freshly cut flowers

OLE GRAF *zefa/Corbis*

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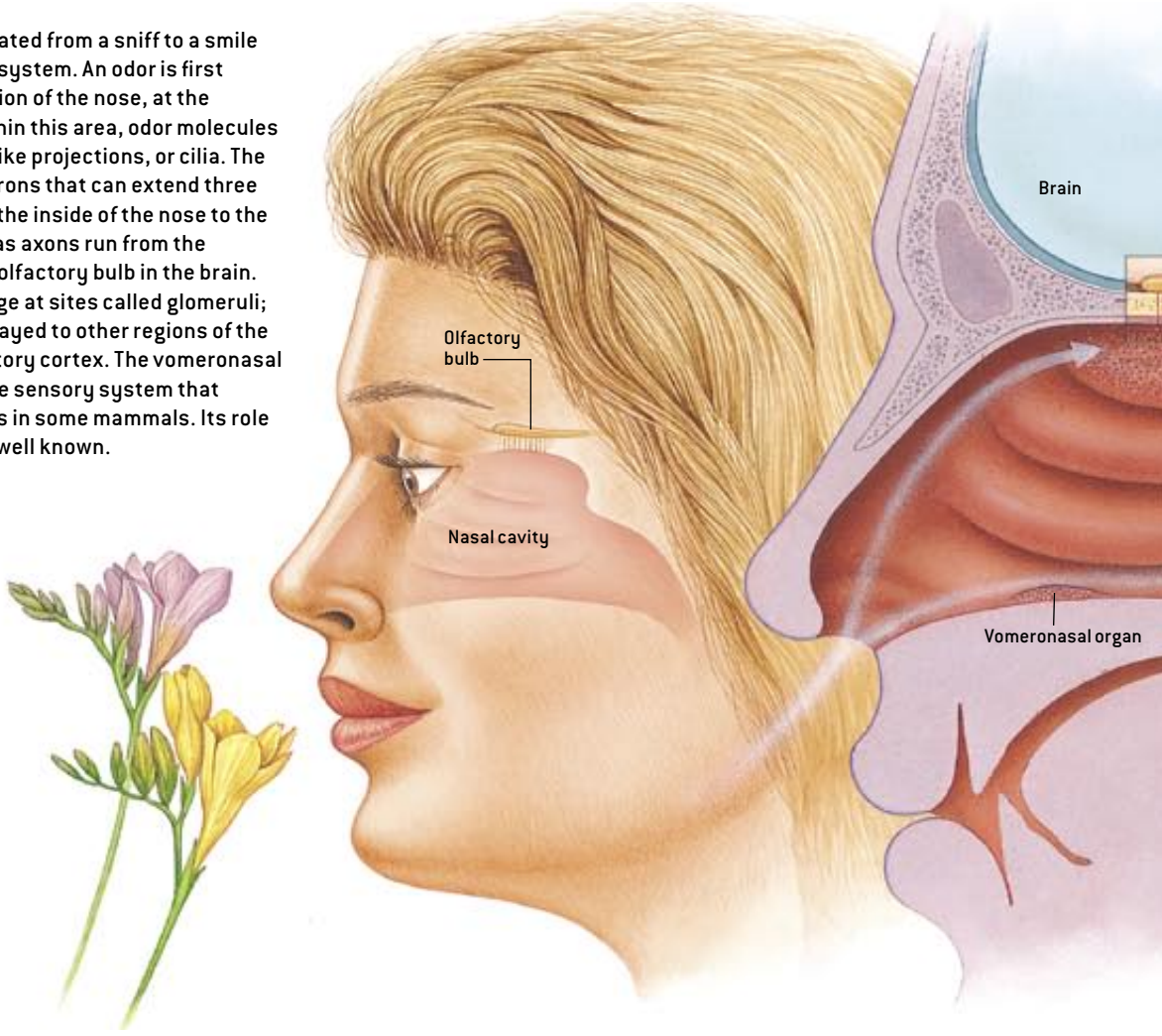
From Blossom to Brain: How Scents Are Sensed

Scent of a flower is translated from a sniff to a smile by the olfactory sensory system. An odor is first detected in the upper region of the nose, at the olfactory epithelium. Within this area, odor molecules bind to receptors on hairlike projections, or cilia. The receptors are part of neurons that can extend three to four centimeters from the inside of the nose to the brain. Structures known as axons run from the neuronal cell body to the olfactory bulb in the brain. In the bulb, axons converge at sites called glomeruli; from there signals are relayed to other regions of the brain, including the olfactory cortex. The vomeronasal organ is part of a separate sensory system that governs innate responses in some mammals. Its role in human behavior is not well known.



to the aversive smell of an angry skunk. Many animals have an even greater sensitivity to odors than humans do: bloodhounds, for example, are legendary for their extraordinary ability to discriminate scents.

The wide spectrum of odors that humans consciously detect prompt varied emotional and cognitive responses. But do humans recognize other smells without a conscious awareness of this perception, and do such odors elicit innate behavioral responses? How does the perception of specific odors lead to appropriate thoughts, memories and behaviors? Whether smell is primal or aesthetic to a species, all organisms must have developed in the course of evolution mechanisms to recognize various odors and transmit this olfactory information from the nose to the brain, where it is decoded to provide an internal representation of the external world.

As molecular biologists studying perception, my colleagues and I have reduced these questions to the level of genes and proteins. We have used these molecules to examine how animals recognize such a diverse array of scents and how the recognition of odors in the nose is translated into a map of odor quality in the brain.

The basic anatomy of the nose and olfactory system has been understood for some time. In mammals, for example, the initial detection of odors takes place at the posterior of the nose, in the small region known as the olfactory epithelium. A scanning electron micrograph of the area reveals two interesting types of cells. In this region, millions of neurons, the signaling cells of sensory systems, provide a direct physical connection between the external world and the brain. From one end of each neuron, hairlike sensors called cilia extend outward and are in direct contact with the air. At the other end of the cell, a fiber known as an axon runs into the

ROBERTO OSTI

THE AUTHOR

RICHARD AXEL is University Professor at Columbia University, where he is also an investigator with the Howard Hughes Medical Institute. Axel is a molecular biologist who now applies the techniques of recombinant DNA and molecular genetics to problems in neurobiology. Most recently he has focused on the molecular biology of perception. In 2004 Axel shared the Nobel Prize in Physiology or Medicine with Linda B. Buck.

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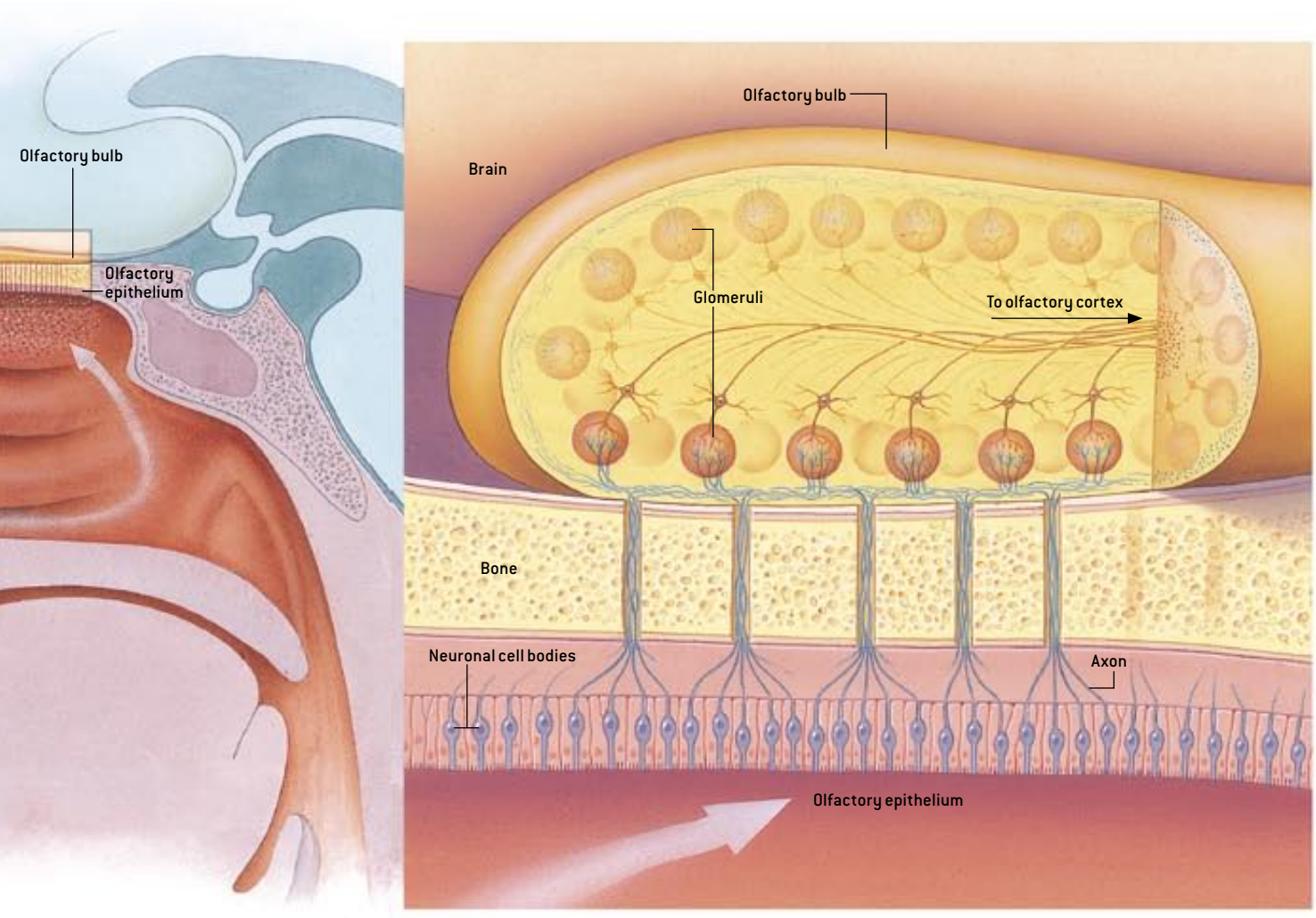

brain. In addition, the olfactory epithelium contains neuronal stem cells, which generate olfactory neurons throughout the life of the organism. Unlike most neurons, which die and are never replaced, the olfactory sensory neurons are continually regenerated.

When an animal inhales odorous molecules, these structures bind to specialized proteins, known as receptor proteins, that extend from the cilia. The binding of odors to these receptors initiates an electrical signal that travels along the axons to the olfactory bulb, which is located in the front of the brain, right behind the nose itself. The olfactory bulb serves as the first relay station for processing olfactory information in the brain; the bulb connects the nose with the olfactory cortex, which then projects to higher sensory centers in the cerebral cortex, the area of the brain that controls thoughts and behaviors.

A Family of Receptors

SOMEWHERE IN THIS ARRANGEMENT lies an intricate logic that the brain uses to identify the odor detected in the nose, distinguish it from others, and trigger an emotional or behavioral response. To probe the organization of the brain, my co-workers and I began where an odor is first physically perceived—at the odor receptor proteins.

Instead of examining odor receptors directly, Linda B. Buck, then a postdoctoral fellow in my laboratory and now a professor at the Fred Hutchinson Cancer Research Center in Seattle, and I set out to find the genes encoding odor receptors. Genes provide the template for proteins, the molecules that carry out the functions of cells. Once we isolate the genes that encode a protein, we can use them as tools to study the structure and function of the odor receptors themselves.

Furthermore, using genes to investigate proteins is much simpler and faster than studying the receptors directly. By artificially manipulating genes, we can easily alter odor receptors in ways that help us understand how the molecules enable the nose and brain to perceive smell. After we understand how the receptors work, we can then study how olfactory information is transmitted to the brain and processed to permit the discrimination of smells.

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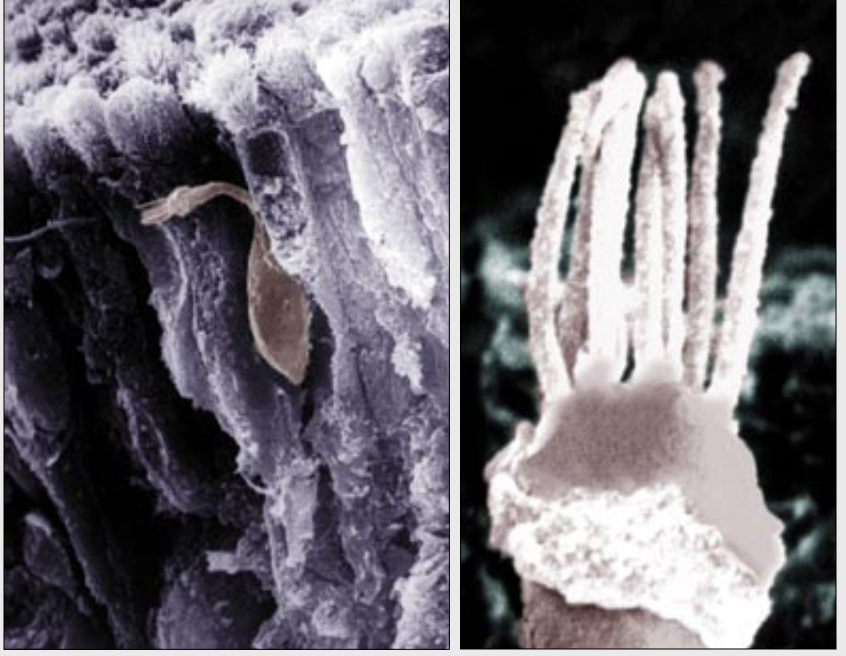

Sensory neuron in the human olfactory epithelium (*left*) is surrounded by support cells and sits over a layer of neuronal stem cells, which generate new olfactory neurons during an organism's life. Hairlike cilia protrude from the tip of an individual neuron (*right*), shown magnified 17,500 times; receptors located on cilia bind to odor molecules. These images were taken by R. M. Costanzo and E. E. Morrison of Virginia Commonwealth University.

Using the technique of gene cloning, we were able to isolate the genes encoding the odor receptors. This family of receptor genes exhibited several properties that suited it to its role in odor recognition. First, the genes encoded proteins that fall squarely within a previously described group of receptors that pass through the cell membrane of the neuron seven times; these receptors activate signaling proteins known as G proteins. Early studies by Doron Lancet of the Weizmann Institute of Science in Rehovot, Israel, and Randall R. Reed of the Johns Hopkins School of Medicine have established that odor receptors, too, use G proteins to initiate the cascade of events resulting in the transmission of an electrical impulse along the olfactory sensory axon.

Second, the genes encoding the odor receptor proteins are active only in olfactory neurons. Although nearly every cell of the body carries a copy of every gene, many genes are expressed only in specialized cells.

The sequence of mammalian genomics reveals about 1,300 odorant receptor genes in mice and 350 genes in humans. (Each type of receptor is expressed in thousands of neurons.) Given that mammalian DNA probably contains around 25,000 genes, this finding indicates that in mice 4 percent of all genes are devoted to the detection of odors, making this the largest gene family thus far identified in mammals. The enormous amount of genetic information devoted to smell perhaps reflects the significance of this sensory system for the survival and reproduction of most mammalian species.

The large family of odor receptors contrasts sharply with the far more restricted repertoire of receptors in the eye. Humans, for example, can discriminate among several hundred hues using only three kinds of receptors on the retina. These photoreceptors detect light in different but overlapping regions of the visible spectrum, so the brain can compare input from all three types of detectors to identify a color. Our data suggest that a small number of odor receptors would not be able to recognize and discriminate the full array of scents that can be perceived by mammals.

Mammals can detect at least 10,000 odors; consequently, each of the 1,300 different receptors must respond to several odor molecules, and each odor must bind to several receptors. For example, the molecules responsible for the scents of jasmine and freshly baked bread are made up of different chemical structures, and each compound activates a distinct set of receptors; to distinguish the smell, the brain must then determine the precise combination of receptors activated by a particular odor.

How does the brain identify which of the 1,300 types of receptors have been turned on? Several scenarios are possible. If every neuron carries all 1,300 types, every neuron would send a signal to the brain every time an odor was sensed. All the engaged receptors would need to contribute some distinctive component to the neuron's signal; the brain could then compare these signals to decipher the identity of the smell. Alternatively, if each neuron features only one type of receptor, the problem of distinguishing which receptor was activated by a particular odor reduces to the problem of identifying which neurons fired. Such a model would greatly simplify the task of the brain in sorting out which of the numerous receptors have been activated.

One Neuron, One Receptor

TO INVESTIGATE WHICH of these two schemes occurs in the detection of smells, we again looked at gene expression in the olfactory neurons. Using the procedure of molecular hybridization, Andrew Chess, John Ngai and Robert Vassar, then all at Columbia University, and I observed that in mammals, each of the 1,300 receptors is expressed in about 0.1 percent of the neurons. In fish, which have 100 odor receptors, each receptor can be found in about 1 percent of the neurons. These results suggest that, in both cases, each neuron may express only one receptor gene. Furthermore, in more recent experiments, Catherine Dulac in my laboratory and Buck independently have used the polymerase chain reaction, which amplifies small parts of DNA, to clone the odor receptor genes that are expressed in individual olfactory neurons. When such receptor genes are isolated from a single neuron, they all appear to be identical. When the same procedure is applied to a collection of neurons, however, hundreds of different receptor genes are obtained. Taken together, these observations indicate that each sensory neuron expresses only one receptor and is therefore functionally distinct.

This simple correlation between receptors and neurons does not explain the much more complex processing that the brain must employ to discriminate an odor. For example,

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how does the brain determine which olfactory neurons have fired? In all other sensory systems, the brain relies on defined spatial patterns of neurons as well as the position of the neurons' ultimate targets to define the quality of a sensation. Perhaps the brain applies a similar logic to the sense of smell.

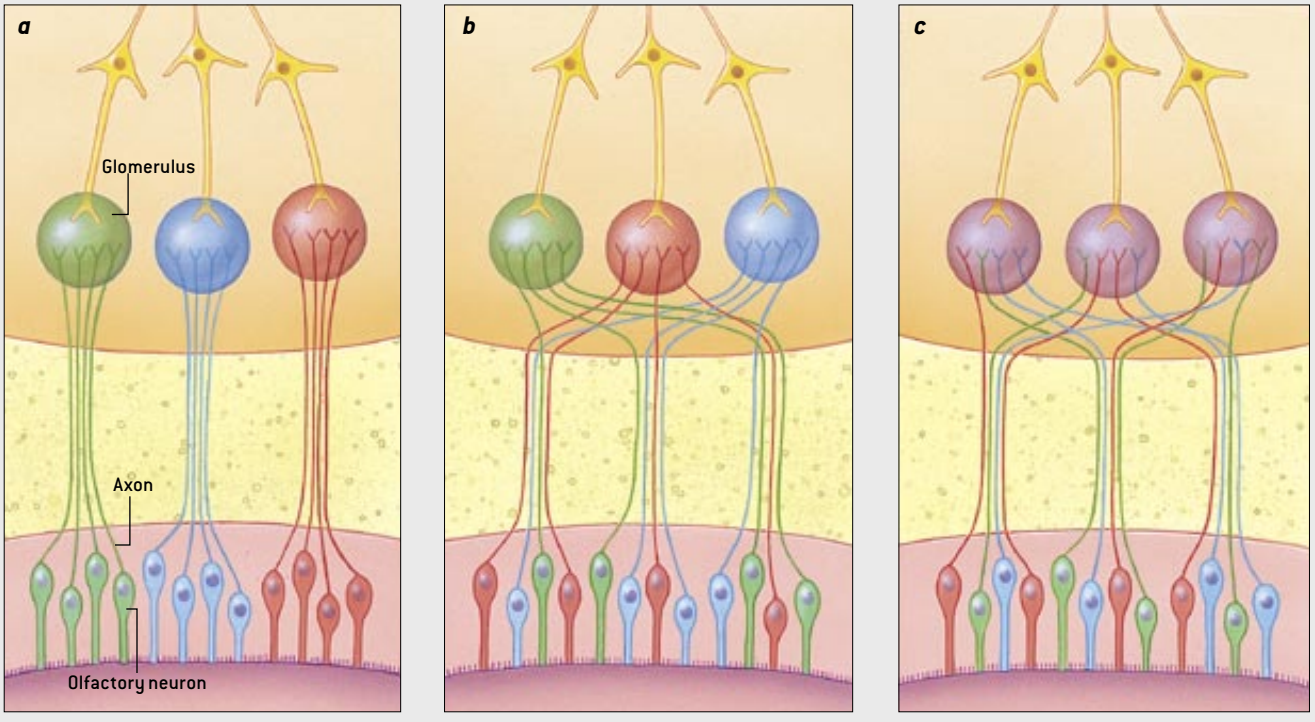
There are a number of potential scenarios for arranging neurons and axons in the nose and brain [*see box below*]. In one model, neurons that bear a given type of receptor would be localized in the olfactory epithelium. Activation of neurons at specific sites would then define the quality of an odor. Alternatively, neurons carrying one type of receptor could be randomly positioned in the epithelium, but their axons would converge on discrete areas in the brain. In this case, exposure to a particular odor would result in defined patterns of activity in the brain. In a third model, both the neurons and their projections to the brain could be arranged randomly. To interpret the scent, the brain would have to use a sophisticated algorithm to decode the random signals.

Some neurons in the nose are spatially segregated according to the scents they detect. Most mammals, including humans, possess a vomeronasal organ that is physically separate from the main olfactory epithelium. The vomeronasal organ detects the pheromones that govern reproductive and social behaviors. The sexual response of male rodents to female rodents, for example, is an innate response, prompted in part by the detection at the vomeronasal organ of pheromones secreted by females. If the neurons in the vomeronasal system are genetically inactivated, the mice can still smell with their main olfactory system, but the inactivation of the vomeronasal organ results in males that attempt to mate with both sexes.

Additionally, as Dulac, Buck and I have independently shown by studying the genes encoding pheromone receptors, the sequence of amino acids (the building blocks of proteins) in the receptors of the vomeronasal organ is completely different from that in the receptors of the main olfactory epithelium. These differences suggest that the two systems may have evolved independently of each other.

Finally, neurons in the main olfactory epithelium project their axons to an area of the brain that is distinct from the region where neurons in the vomeronasal organ send nerve impulses. Consequently, signals from these two regions of the nose produce very different behavioral responses. The neurons of the vomeronasal organ bypass the cognitive centers of the brain and send signals directly to those areas that control innate behavioral and emotional responses. In contrast, the main epithelium sends signals to higher centers in the olfactory cortex that elicit more measured responses.

Models for Nose-Brain Signaling



Patterns of neurons can help the brain interpret a smell. Several arrangements are possible. In one scenario (*a*), neurons that contain a particular type of receptor (*indicated here by color*) would be localized in the olfactory epithelium; in this way, the brain could identify an odor by determining what area of the olfactory epithelium was activated by the smell. Alternatively (*b*), neurons may be arranged randomly throughout the epithelium, but their axons may converge on localized regions of the olfactory bulb known as glomeruli. An odor would therefore be identified by a characteristic pattern of activity in the glomeruli. Finally (*c*), both the neurons and their axons may be arranged randomly.

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Organized Axons

THE ANATOMICAL SEGREGATION of these two functionally distinct olfactory systems immediately prompted us to examine whether neurons within the main olfactory system itself also exploit spatial segregation to define the quality of an odor. Some of this spatial organization is well known: each neuron projects a single, unbranched axon toward the brain. As the collection of axons emerges from the olfactory epithelium, about 10 million axons come together to form the olfactory nerve, which then enters the brain. Once inside the brain, groups of 10,000 axons converge at sites called glomeruli in the olfactory bulb. In the glomeruli the axons communicate with neurons that project to higher centers in the brain.

Experiments done by Vassar in my lab at Columbia, as well as independent research carried out by Buck, showed that the olfactory epithelium is divided into four broad regions according to the types of receptors found in each zone. Despite this coarse organization, the most important feature of this arrangement is the random distribution of receptors within each region. Because we were unable to detect a more precise spatial pattern of neurons in the epithelium, we searched for a pattern in the projections of axons into the brain.

If such a pattern is indeed employed, neurons expressing a given receptor, though randomly distributed throughout a region of the epithelium, must project their axons to a small number of glomeruli. Several pieces of evidence support this model.

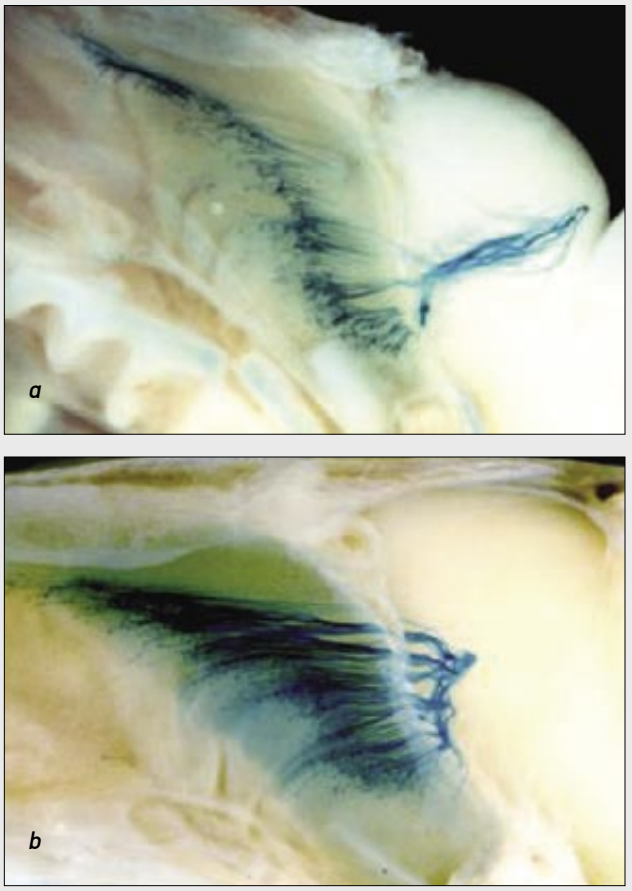
First, the number of glomeruli is roughly the same as the number of types of receptors; because each neuron expresses only one receptor, each type of neuron may connect to a characteristic glomerulus. Second, physiological experiments have revealed that different odors elicit distinct patterns of activity in the brain. For example, Gordon M. Shepherd and his colleagues at Yale University established that exposure of newborn rodents to their mother's milk led to activity in restricted regions of the olfactory bulb.

Similarly, John S. Kauer of Tufts University used voltage-sensitive dyes to show that the pattern of activity in the olfactory bulb is distinct for various odors. Furthermore, electrophysiological studies by Kensaku Mori, now at the University of Tokyo, directly demonstrated that distinct glomeruli are activated by different odors. More recent imaging studies by a number of labs using different animals have revealed that different odors elicit distinct and invariant patterns of glomerular activity.

My colleagues and I devised two molecular approaches to study the spatial segregation of neurons and axons. First, Vassar, Steve K. Chao and Leslie B. Vosshall, working in my lab, modified the technique of molecular hybridization used in previous work so that we could examine receptor RNA in the tips of the axons, where they converge in the olfactory bulb. These experiments, as well as independent work by Buck, indicated that neurons expressing a given receptor project to one or, at most, a few glomeruli among the thousands within the olfactory bulb. Moreover, the positions of the glomeruli are fixed, assuring that a given odor will elicit the same pattern of activity in the brains of all animals in a species.

In another approach, Peter Mombaerts, now at the Rockefeller University, and Fan Wang, now at Duke University, and I have genetically altered mice, breeding experimental animals in which neurons that activate a specific receptor were dyed blue. Our procedure involves isolating a gene for one of the odor receptors and then attaching to it a second, marker gene. This marker gene, which will become active whenever the odor receptor gene is expressed, triggers a chemical reaction that turns the neuron and its axon blue. The modified gene is inserted into cells that are then introduced into a mouse embryo. In the resulting mice that develop, neurons that make this particular receptor appear blue, allowing us

Converging Neurons



Blue neurons reveal the pathways of sensory information from the olfactory epithelium in the nose (*left side of photographs*) to the olfactory bulb in the brain (*right side*). By genetically modifying odor receptor genes in mice, the author and his colleagues cause the neurons that bear a particular type of receptor to turn deep blue. Neurons that express different receptors converge at different points in the brain, resulting in a highly stereotyped map. For example, randomly positioned neurons expressing the M12 receptor converge at one point (*a*), whereas neurons expressing the P2 receptor converge at another point (*b*).

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to see where the cells are located [*see box on opposite page*].

We examined the olfactory epithelia and brains of the mice and observed that about one in 1,000 neurons were blue. Most important, individual axons stretching from the neurons could be identified and followed into the brain. The blue axons projected to only two of the 2,000 glomeruli in the olfactory bulb. These experiments provide convincing visual evidence that neurons that activate one type of receptor—and therefore respond to a limited number of odors—project their axons to a small number of glomeruli in the brain. Because the glomeruli in the olfactory bulb are differentially sensitive to specific odors, and the positions of the individual glomeruli are topologically defined, the olfactory bulb provides a two-dimensional map that identifies which of the numerous receptors have been activated in the nose. We believe a given odor will activate a characteristic combination of glomeruli in the olfactory bulb; signals from the glomeruli are then transmitted to the olfactory cortex, where they must be processed to allow odor discrimination.

Decoding the Signal

IN RECENT STUDIES, we have examined the relation between this anatomical map and the functional representation of olfactory information in the brain. To do this, we turned to the fruit fly *Drosophila melanogaster,* which exhibits complex behaviors controlled by an olfactory system that is anatomically and genetically simpler than that of vertebrates. We first demonstrated that the anatomical organization in the fruit fly is remarkably similar to that of the olfactory system of mammals—suggesting that the mechanism of odor discrimination has been shared despite the 600 million years of evolution separating insects from mammals.

An understanding of the logic of odor perception requires functional analysis to identify odor-evoked patterns of activity in neural assemblies in the brain and ultimately the relevance of these patterns to odor discrimination. We have used the procedure known as two-photon calcium imaging to examine the relation between the anatomical map and the functional map in the fly equivalent of the olfactory bulb, the antennal lobe. Jing Wang and Allan Wong, in my lab, developed an isolated *Drosophila* brain preparation that is responsive to odor stimulation for several hours. These experiments allow us to observe the functional map of odor representation in brain space. Different odors each elicit different patterns of glomerular activation in the fly brain, and these patterns are conserved among different animals. Imaging experiments in vertebrates similarly reveal a functional representation of the anatomical map. Thus, the pattern of glomerular activation may confer a signature for different odors in the brain.

This view of olfactory perception shares several basic features with perception in other sensory systems. For example, in vision the brain analyzes an image by interpreting the individual components: form, location, movement, color. The unity of an image is accomplished by reconstructing the signals in the visual centers of the higher cortex. In comparison, the brain analyzes an odor by dissecting the structural features of the scent. The odor is then reconstructed by the olfactory cortex.

Olfactory bulb of a rat is seen in cross section in this micrograph. The two white spots indicate where axons that bear a specific receptor gene converge. Because each axon projects to a characteristic location in the olfactory bulb, the bulb provides a two-dimensional map of odor quality, which the olfactory cortex employs to decipher an odor.

But how does the olfactory cortex, which receives signals from the olfactory bulb, decode the map provided by the olfactory bulb? This question is one of the central and most elusive problems in neurobiology. It seems likely that some form of spatial segregation, similar to that seen in the olfactory bulb but undoubtedly far more complex, will be maintained as the signals project into the cortex. This arrangement, however, merely places the problem of interpreting spatial information one level beyond the olfactory bulb, in the cortex. How does the cortex prompt the range of emotional or behavioral responses that smells often provoke? To what extent is the recognition of odors in humans conscious or nonconscious, and how much of behavior or mood is governed by the perception of odors in our environment? We have only begun to explore the logic of smell and how it can evoke the "vast structure of recollection." SA

MORE TO EXPLORE

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STEVE K. CHAD AND ROBERT VASSAR; COURTESY OF *CELL*

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Hearing Colors, TASTING SHAPES

People with **synesthesia**—whose senses blend together—are providing valuable clues to understanding the organization and functions of the brain

BY VILAYANUR S. RAMACHANDRAN AND EDWARD M. HUBBARD

When Matthew Blakeslee shapes hamburger patties with his hands, he experiences a vivid bitter taste in his mouth. Esmerelda Jones (a pseudonym) sees blue when she listens to the note C sharp played on the piano; other notes evoke different hues—so much so that the piano keys are actually color-coded. And when Jeff Coleman looks at printed black numbers, he sees them in color, each a different hue. Blakeslee, Jones and Coleman are among a handful of otherwise normal people who have synesthesia. They experience the ordinary world in extraordinary ways and seem to inhabit a mysterious no-man's-land between fantasy and reality. For them the senses—touch, taste, hearing, vision and smell—get mixed up instead of remaining separate.

Modern scientists have known about synesthesia since 1880, when Francis Galton, a cousin of Charles Darwin, published a paper in *Nature* on the phenomenon. But most have brushed it aside as fakery, an artifact of drug use or a mere curiosity. About seven years ago, however, we and others began to uncover brain processes that could account for synesthesia. Along the way, we also found new clues to some of the most mysterious aspects of the human mind, such as the emergence of abstract thought and metaphor.

A common explanation of synesthesia is that the affected people are simply experiencing childhood memories and associations. Maybe a person had played with refrigerator magnets as a child, and the number 5 was red and 6 was green. This

DAVID EMMITE

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theory does not answer why only some people retain such vivid sensory memories, however. You might *think* of cold when you look at a picture of an ice cube, but you probably do not feel cold, no matter how many encounters you may have had with ice and snow during your youth.

Another prevalent idea is that synesthetes are merely being metaphorical when they describe the note C sharp as "red" or say that chicken tastes "pointy"—just as you and I might speak of a "loud" shirt or "sharp" cheddar cheese. Our ordinary language is replete with such sense-related metaphors, and perhaps synesthetes are just especially gifted in this regard.

To determine whether an effect is truly perceptual, psychologists often use a simple test called pop-out or segregation. If you look at a set of tilted lines scattered amid a forest of vertical lines, the tilted lines stand out. Indeed, you can instantly segregate them from the background and group them mentally to form, for example, a separate triangular shape. Similarly, if most of a background's elements were green dots and you were told to look for red targets, the red ones would pop out. On the other hand, a set of black 2's scattered among 5's of the same color almost blend in [*see box on page 81*]. It is hard to discern the 2's without engaging in an item-by-item inspection of numbers, even though any individual number is just as clearly different from its neighbors as a tilted line is from a straight line. We thus may conclude that only certain primitive, or elementary, features, such as color and line orientation, can provide a basis for grouping. More complex perceptual tokens, such as numbers, cannot.

We wondered what would happen if we showed the mixed numbers to synesthetes who experience, for instance, red when they see a 5 and green with a 2. We arranged the 2's so that they formed a triangle.

When we conducted these tests with volunteers, the answer was crystal clear. Unlike normal subjects, synesthetes correctly reported the shape formed by groups of numbers up to 90 percent of the time (exactly as nonsynesthetes do when the numbers actually have different colors). This result proves that the induced colors are genuinely sensory and that synesthetes are not just making things up. It is impossible for them to fake their success.

Visual Processing

CONFIRMATION that synesthesia is real brings up the question, Why do some people experience this weird phenomenon? Our experiments lead us to favor the idea that synesthetes are experiencing the result of some kind of cross wiring in the brain. This basic concept was initially proposed about 100 years ago, but we have now identified where and how such cross wiring might occur.

An understanding of the neurobiological factors at work requires some familiarity with how the brain processes visual information. After light reflected from a scene hits the cones (color receptors) in the eye, neural signals from the retina travel to area 17, in the occipital lobe at the back of the brain. There the image is processed further within local clusters, or blobs, into such simple attributes as color, motion, form and depth. Afterward, information about these separate features is sent forward and distributed to several far-flung regions in the temporal and parietal lobes. In the case of color, the information goes to area V4 in the fusiform gyrus of the temporal lobe. From there it travels to areas that lie farther up in the hierarchy of color centers, including a region near a patch of cortex called the TPO (for the junction of the *t*emporal, *p*arietal and *o*ccipital lobes). These higher areas may be concerned with more sophisticated aspects of col-

Confirmation that synesthesia is real brings up the question, Why do some people experience it?

We began trying to find out whether synesthesia is a genuine sensory experience in 1999. This deceptively simple question had plagued researchers in the field for decades. One natural approach is to start by asking the subjects outright: "Is this just a memory, or do you actually see the color as if it were right in front of you?" When we asked this question, we did not get very far. Some subjects did respond, "Oh, I see it perfectly clearly." But a more frequent reaction was, "I kind of see it, kind of don't" or "No, it is not like a memory. I see the number as being clearly red, but I also *know* it isn't; it's black. So it must be a memory, I guess."

Overview/*Synesthesia*

- Synesthesia (from the Greek roots *syn,* meaning "together," and *aisthesis,* or "perception") is a condition in which people experience the blending of two or more senses.
- Perhaps it occurs because of cross activation, in which two normally separate areas of the brain elicit activity in each other.
- As scientists explore the mechanisms involved in synesthesia, they are also learning about how the brain in general processes sensory information and uses it to make abstract connections between seemingly unrelated inputs.

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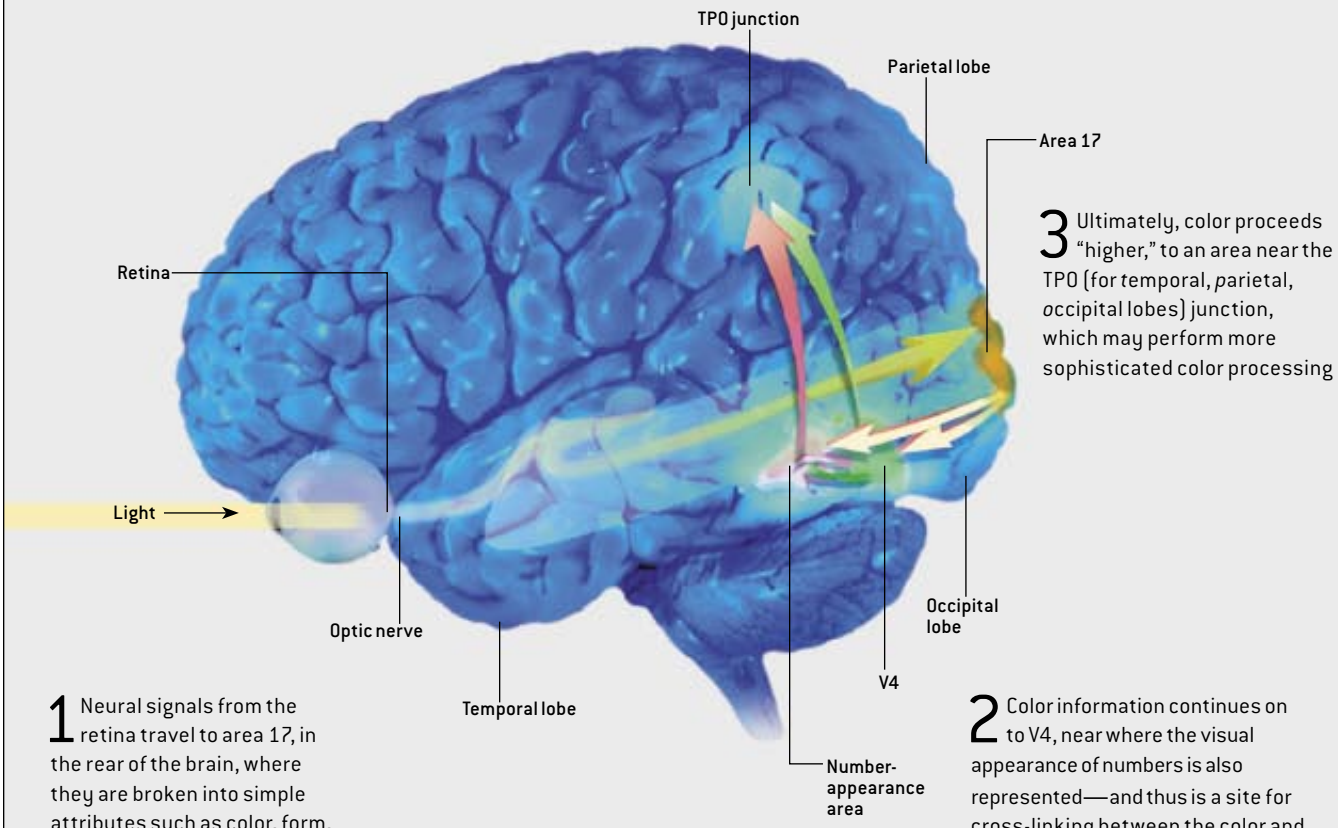
Mixed Signals

In one of the most common forms of synesthesia, looking at a number evokes a specific hue. This phenomenon apparently occurs because brain areas that normally do not interact when processing numbers or colors do activate each other in synesthetes.


TPO junction
Parietal lobe
Area 17
3 Ultimately, color proceeds "higher," to an area near the TPO (for temporal, parietal, occipital lobes) junction, which may perform more sophisticated color processing
Retina
Light
Optic nerve
Temporal lobe
Occipital lobe
V4
Number-appearance area
1 Neural signals from the retina travel to area 17, in the rear of the brain, where they are broken into simple attributes such as color, form, motion and depth
2 Color information continues on to V4, near where the visual appearance of numbers is also represented—and thus is a site for cross-linking between the color and number areas (*pink* and *green arrows*)

or processing. For example, leaves look as green at dusk as they do at midday, even though the mix of wavelengths reflected from them is very different.

Numerical computation, too, seems to happen in stages. An early step also takes place in the fusiform gyrus, where the actual shapes of numbers are represented, and a later one occurs in the angular gyrus, a part of the TPO that is concerned with numerical concepts such as ordinality (sequence) and cardinality (quantity). When the angular gyrus is damaged by a stroke or a tumor, the patient can still identify numbers but can no longer perform multiplication. After damage to another nearby region, subtraction and division may be lost, while multiplication may survive (perhaps because it is learned by rote). In addition, brain-imaging studies in humans strongly hint that visually presented letters of the alphabet or numbers (graphemes) activate cells in the fusiform gyrus, whereas the sounds of the syllables (phonemes) are processed higher up, once again in the general vicinity of the TPO.

Because both colors and numbers are processed initially in the fusiform gyrus and subsequently near the angular gyrus, we suspected that number-color synesthesia might be caused by cross wiring between V4 and the number-appearance area (both within the fusiform) or between the higher color area and the number-concept area (both in the TPO).

Other, more exotic forms of the condition might result from similar cross wiring of different sensory-processing regions. That the hearing center in the temporal lobes is also close to the higher brain area that receives color signals from V4 could explain sound-color synesthesia. Similarly, Matthew Blakeslee's tasting of touch might occur because of cross wiring between the taste cortex in a region called the insula and an adjacent cortex representing touch by the hands. Another synesthete with taste-induced touch describes the flavor of mint as cool glass columns.

Taste can also be cross-wired to hearing. For example, one synesthete reports that the spoken Lord's Prayer "tastes" mostly of bacon. In addition, the name "Derek" tastes of earwax,

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whereas the name "Tracy" tastes like a flaky pastry.

Assuming that neural cross wiring does lie at the root of synesthesia, why does it happen? We know that synesthesia runs in families, so it has a genetic component. Perhaps a mutation causes connections to emerge between brain areas that are usually segregated. Or maybe the mutation leads to defective pruning of preexisting connections between areas that are normally connected only sparsely. If the mutation were to be expressed (that is, to exert its effects) in some brain areas but not others, this patchiness might explain why some synesthetes conflate colors and numbers, whereas others see colors when they hear phonemes or musical notes. People who have one type of synesthesia are more likely to have another, and within some families, different members will have different types of synesthesia; both facts add weight to this idea.

an inhibitor—would also cause activity in one area to elicit activity in a neighbor. Such cross activation could, in theory, also occur between widely separated areas, which would account for some of the less common forms of synesthesia.

Support for cross activation comes from other experiments, some of which also help to explain the varied forms synesthesia can take. One takes advantage of a visual phenomenon known as crowding [*see box on opposite page*]. If you stare at a small plus sign in an image that also has a number 5 off to one side, you will find that it is easy to discern that number, even though you are not looking at it directly. But if we now surround the 5 with four other numbers, such as 3's, then you can no longer identify it. It looks out of focus. Volunteers who perceive normally are no more successful at identifying this number than mere chance. That is not because things get fuzzy in the periphery of vision. After all, you could see the 5 perfectly clearly when it was not surrounded by 3's. You cannot identify it now because of limited attentional resources. The flanking 3's somehow distract your attention away from the central 5 and prevent you from seeing it.

A big surprise came when we gave the same test to two synesthetes. They looked at the display and made remarks like, "I cannot see the middle number. It's fuzzy, but it looks red, so I guess it must be a 5." Even though the middle number did not consciously register, it seems that the brain was nonetheless processing it somewhere. Synesthetes could then use this color to deduce intellectually what the number was. If our theory is right, this finding implies that the number is processed in the fusiform gyrus and evokes the appropriate color *before* the stage at which the crowding effect occurs in the brain; paradoxically, the result is that even an "invisible" number can produce synesthesia for some synesthetes.

Another finding we made also supports this conclusion. When we reduced the contrast between the number and the background, the synesthetic color became weaker until, at low contrast, subjects saw no color at all, even though the number was perfectly visible. Whereas the crowding experiment shows that an invisible number can elicit color, the contrast experiment conversely indicates that viewing a number does not guarantee seeing a color. Perhaps low-contrast numbers activate cells in the fusiform adequately for conscious perception of the number but not enough to cross-activate the color cells in V4.

Synesthesia is much more common in creative people than in the general population.

Finally, we found that if we showed synesthetes Roman numerals, a V, say, they saw no color—which suggests that it is not the numerical *concept* of a number, in this case 5, but the grapheme's visual appearance that drives the color. This observation, too, implicates cross activation within the fusiform gyrus itself in number-color synesthesia, because that structure is mainly involved in analyzing the visual shape, not the high-level meaning, of the number. One intriguing twist: Imagine an image with a large 5 made up of little 3's; you can see either the "forest" (the 5) or focus minutely on the "trees" (the 3's). Two synesthete subjects reported that they saw the color switch, depending on their focus. This test implies that even though synesthesia can arise as a result of the visual appearance alone—

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not the high-level concept—the manner in which the visual input is categorized, based on attention, is also critical.

But as we began to recruit other volunteers, it soon became obvious that not all synesthetes who colorize their world are alike. In some, even days of the week or months of the year elicit colors.

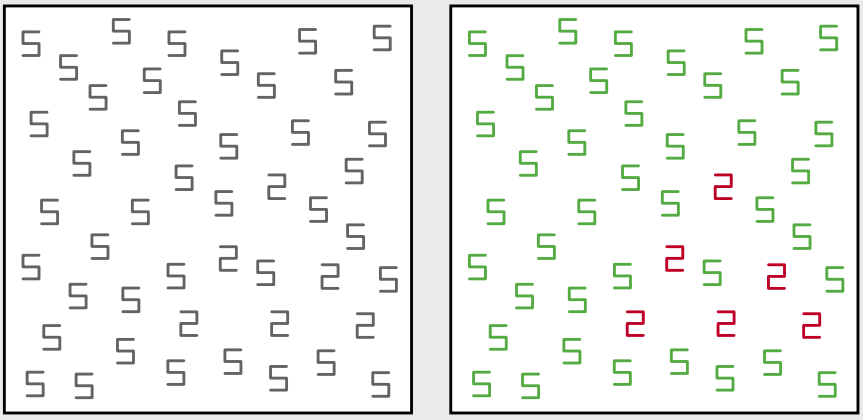
The only thing that days of the week, months and numbers have in common is the concept of numerical sequence, or ordinality. For certain synesthetes, perhaps it is the abstract concept of numerical sequence that drives the color, rather than the visual appearance of the number. Could it be that in these individuals, the cross wiring occurs between the angular gyrus and the higher color area near the TPO instead of between areas in the fusiform? If so, that interaction would explain why even abstract number representations, or the *idea* of the numbers elicited by days of the week or months, will strongly evoke specific colors. In other words, depending on where in the brain the synesthesia gene is expressed, it can result in different types of the condition—"higher" synesthesia, driven by numerical concept, or "lower" synesthesia, produced by visual appearance alone. Similarly, in some lower forms, the visual appearance of a letter might generate color, whereas in higher forms it is the *sound*, or phoneme, summoned by that letter; phonemes are represented near the TPO.

We also observed one case in which we believe cross activation enables a color-blind synesthete to see numbers tinged with hues he otherwise cannot perceive; charmingly, he refers to these as "Martian colors." Although his retinal color receptors cannot process certain wavelengths, we suggest that his brain color area is working just fine and being cross-activated when he sees numbers.

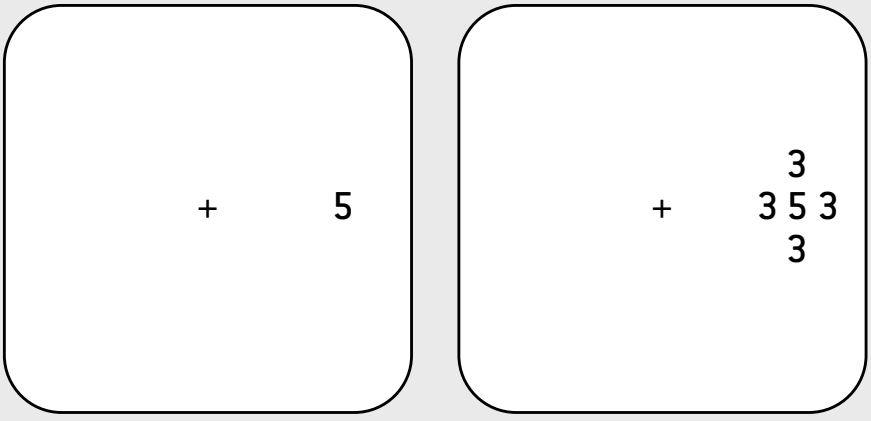
In brain-imaging experiments we conducted with Geoffrey M. Boynton of the Salk Institute for Biological Studies in San Diego, we obtained evidence of local activation of the color area V4 in a manner predicted by our cross-activation theory of synesthesia. (The late Jeffrey A. Gray of the Institute of Psychiatry in London and his colleagues reported similar results.) On presenting black and white numbers and letters to synesthetes, brain activation increased not only in the number area—as it would in normal subjects—but also in the color area. Our group also observed differences between types of synesthetes. Subjects with lower synesthesia showed much greater activation in earlier stages of color processing than did control subjects. In contrast, higher synesthetes show less activation at these earlier levels.

Color-Coded World

In a test of visual-segregation capabilities, synesthetes who link a specific hue with a given number can instantly see an embedded pattern in an image with black numbers scattered on a white page. Whereas a person with normal perception must undertake a digit-by-digit search to pick out, in this example, 2's amid 5's (*left*), the triangle-shaped group of 2's pops out for an individual with synesthesia (*right*).



"Invisible" numbers show up for synesthetes in a perceptual test. When a person stares at a central object, here a plus sign, a single digit off to one side is easy to see with peripheral vision (*left*). But if the number is surrounded by others (*right*), it appears blurry—invisible—to the average person. In contrast, a synesthete could deduce the central number by the color it evokes.



Floating Numbers

GALTON DESCRIBED another intriguing form of synesthesia, in which numbers seem to occupy specific locations in space. Different numbers occupy different locations, but they are arranged sequentially in ascending order on an imaginary "number line." The number line is often convoluted in an elaborate manner—sometimes even doubling back on itself so that, for example, 2 might be "closer" to 25 than to 4. If the subject tilts his head, the number line also may tilt. Some synes-

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thetes claim to be able to "wander" the number landscape and are even able to shift vantage point, to "inspect" hidden parts of the line or see it from the other side so the numbers appear reversed. In some individuals, the line even extends into three-dimensional space. These strange observations reminded us of neuroscientist Warren S. McCulloch's famous question, "What is a number, that a man may know it, and a man, that he may know a number?"

How do we know the number line is a genuine perceptual construct, not something the subject is just imagining or making up? One of us (Ramachandran), working in collaboration with U.C.S.D. graduate student Shai Azoulai, tested two number-line synesthetes. We presented 15 numbers (out of 100) simultaneously on the screen for 30 seconds and asked the subjects to memorize them. In one condition (called the congruent condition), the numbers fell where they were "supposed" to on the virtual number line. In the second condition, the numbers were placed in incorrect locations (the incongruent condition). When tested after 90 seconds, the subjects' memory for the numbers in the congruent condition was significantly better than in the incongruent condition. This is the first objective proof, since Galton observed the effect, that number lines are genuine in that they can affect performance in a cognitive task.

In a related experiment, we used the well-known numerical distance effect. When normal people are asked which of two numbers is bigger, they respond faster when the numbers are farther apart (for example, 4 and 9) than when they are close together (say, 3 and 4). This phenomenon implies that the brain does not represent numbers in a kind of look-up table, as in a computer, but rather spatially in sequence. Adjacent numbers are more easily confused, and therefore more difficult to make comparisons with, than numbers that are farther apart. The astonishing thing is that in one subject with a convoluted number line we found that it was not the numerical distance alone that determined performance, but spatial distance on the synesthetic screen. If the line doubled back on itself, then 4 might be more difficult to tell apart from, say, 19 than from 6! Here again was evidence for the reality of number lines.

Number lines can influence arithmetic. One of our subjects reported that even simple arithmetic operations such as subtraction or division were more difficult across the kinks or inflections of the line than across straight sections. This result suggests that numerical sequence (whether for numbers or calendars) is represented in the angular gyrus of the brain, which is known to be involved in arithmetic.

Why do some people have convoluted number lines? We suggest the effect occurs because one of the main functions of the brain is to "remap" one dimension onto another. For instance, numerical concept (size of the number) is mapped in a systematic manner onto the sequentiality represented in the angular gyrus. Usually this effect is a vague left-to-right, straight-line remapping. But if a mutation occurs that adversely influences this remapping, a convoluted representation results. Such quirky spatial representations of numbers may also enable geniuses like Albert Einstein to see hidden relations between numbers that are not obvious to lesser mortals like us.

A Way with Metaphor

OUR INSIGHTS into the neurological basis of synesthesia could help explain some of the creativity of painters, poets and novelists. According to one study, the condition is much more common in creative people than in the general population.

One skill that many creative people share is a facility for using metaphor ("It is the east, and Juliet is the sun"). It is as if their brains are set up to make links between seemingly unrelated domains—such as the sun and a beautiful young woman. In other words, just as synesthesia involves making arbitrary links between seemingly unrelated perceptual entities such as colors and numbers, metaphor involves making links between seemingly unrelated conceptual realms. Perhaps this is not just a coincidence.

Numerous high-level concepts are probably anchored in specific brain regions, or maps. If you think about it, there is nothing more abstract than a number, and yet it is represented, as we have seen, in a relatively small brain region, the angular gyrus. Let us say that the mutation we believe brings about synesthesia causes excess communication among different brain maps—small patches of cortex that represent specific perceptual entities, such as sharpness or curviness of shapes or, in the case of color maps, hues. Depending on where and how widely in the brain the trait was expressed, it could lead to both synesthesia and a propen-

The Puzzle of Language

If asked which of the two figures above is a "bouba" and which is a "kiki," 98 percent of all respondents choose the blob as a bouba and the other as a kiki. The authors argue that the brain's ability to pick out an abstract feature in common—such as a jagged visual shape and a harsh-sounding name—could have paved the way for the development of metaphor and perhaps even a shared vocabulary.

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sity toward linking seemingly unrelated concepts and ideas—in short, creativity. This might explain why the apparently useless synesthesia gene has survived in the population.

In addition to clarifying why artists might be prone to experiencing synesthesia, our research suggests that we all have some capacity for it and that this trait may have set the stage for the evolution of abstraction—an ability at which humans excel. The TPO (and the angular gyrus within it), which plays a part in the condition, is normally involved in cross-modal synthesis. It is the brain region where information from touch, hearing and vision is thought to flow together to enable the construction of high-level perceptions. For example, a cat is fluffy (touch), it meows and purrs (hearing), it has a certain appearance (vision) and odor (smell), all of which are derived simultaneously by the memory of a cat or the sound of the word "cat."

Could it be that the angular gyrus—which is disproportionately larger in humans than in apes and monkeys—evolved originally for cross-modal associations but then became co-opted for other, more abstract functions such as metaphors?

Consider two drawings, originally designed by psychologist Wolfgang Köhler [*see box on opposite page*]. One looks like an inkblot and the other, a jagged piece of shattered glass. When we ask, "Which of these is a 'bouba,' and which is a 'kiki'?" 98 percent of people pick the inkblot as a bouba and the other as a kiki. Perhaps that is because the gentle curves of the amoeba-like figure metaphorically mimic the gentle undulations of the sound "bouba," as represented in the hearing centers in the brain as well as the gradual inflection of the lips as they produce the curved "boo-baa" sound.

In contrast, the waveform of the sound "kiki" and the sharp inflection of the tongue on the palate mimic the sudden changes in the jagged visual shape. The only thing these two kiki features have in common is the abstract property of jaggedness that is extracted somewhere in the vicinity of the TPO, probably in the angular gyrus. In a sense, perhaps we are all closet synesthetes.

So the angular gyrus performs a very elementary type of abstraction—extracting the common denominator from a set of strikingly dissimilar entities. We do not know exactly how it does this job. But once the ability to engage in cross-modal abstraction emerged, it might have paved the way for the more complex types of abstraction.

When we began our research on synesthesia, we had no inkling of where it would take us. Little did we suspect that this eerie phenomenon, long regarded as a mere curiosity, might offer a window into the nature of thought. SA

Common Questions

Are there different types of synesthesia?
Science counts about 50. The condition runs in families and may be more common in women and creative people; at least one person in 200 has synesthesia. In the most prevalent type, looking at numbers or listening to tones evokes a color. In another kind, each letter is associated with the male or female sex—an example of the brain's tendency to split the world into binary categories.

If a synesthete associates a color with a single letter or number, what happens if he looks at a pair of letters, such as "ea," or double digits, as in "25"?
He sees colors that correspond with the individual letters and numbers. If the letters or numbers are too close physically, however, they may cancel each other out (color disappears) or, if the two happen to elicit the same color, enhance each other.

Does it matter whether letters are uppercase or lowercase?
In general, no. But people have sometimes described seeing less saturated color in lowercase letters, or the lowercase letters may appear shiny or even patchy.

How do entire words look?
Often the color of the first letter spreads across the word; even silent letters, such as the "p" in "psalm," cause this effect.

What if the synesthete is multilingual?
One language can have colored graphemes, but a second (or additional others) may not, perhaps because separate tongues are represented in different brain regions.

What about when the person mentally pictures a letter or number?
Imagining can evoke a stronger color than looking at a real one. Perhaps that exercise activates the same brain areas as does viewing real colors—but because no competing signals from a real number are coming from the retina, the imagined one creates a stronger synesthetic color.

Does synesthesia improve memory?
It can. The late Russian neurologist Aleksandr R. Luria described a mnemonist who had remarkable recall because all five of his senses were linked. Even having two linked senses may help. *—V.S.R. and E.M.H.*

MORE TO EXPLORE

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